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CLINICAL EVALUATION OF PREFRONTAL LOBOTOMY

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A survey made by the National Institute of Mental Health indicates that by the end of 1949 about 10,000 persons in the United States had undergone lobotomy or some form of surgical ablation of the frontal lobes of the brain for mental illness. The number of operations of this type had increased annually during each of the five preceding years. Thus, the interest in lobotomy has gained momentum since the procedure was introduced by Egas Moniz late in 1935.

The extensive surgical, anatomic, physiological and psychological studies that have emanated from the investigation of patients treated by this method have led to the collection of considerable new knowledge in regard to the functions of the frontal lobe and also have made apparent many deficiencies in that knowledge; for example, the majority of psychological techniques in use at present in the study of such patients are incapable of yielding information about deficits in intelligence on a high level that result from the operative procedure, although the failures in social adaptability and abstract thinking are evident to close family observers, social workers, and clinicians. In addition, physicians have been made aware of weaknesses in knowledge of the usual outcome of mental illnesses and of the noncritical manner in which therapeutic claims are frequently made in the field of psychiatry. Most of the reports on results of lobotomy published prior to 1947 failed to indicate whether the patients so treated were hospitalized or to give the duration of illness and hospitalization prior to lobotomy. No comparisons were made between the results obtained by lobotomy after long periods of follow-up and the known expectations for patients who did not undergo such operations. In some reports, outcome was defined successfully by stating the occupational adjustment of the patients; however, observations on the preoperative and preillness status of the patients were not made. In other reports, the outcome has been defined in terms of modifications of specific behavioral problems. From review of these reports it became apparent that the earlier statistical methods practiced in reporting of the outcome of the use of prefrontal lobotomy provided an illusory impression of the worthiness of the procedure that could not be confirmed by comparison of the data available with earlier statistics on the long-term expectations in psychiatric illnesses. Detailed case reports, including long periods of postoperative observation, did suggest that many chronically ill patients were restored to a productive life in the community as a result of this surgical procedure. Even from these reports, it is not possible to decide what proportion of patients benefited as the result of the operation and what proportion benefited as the result of preoperative attention, which has a psychotherapeutic effect. The indication that the latter factor cannot be ignored was made apparent in the Greystone Park investigation of topectomy, in which 3 of 24 chronically ill control patients, who were treated in every respect as the group that were subsequently operated on, recovered sufficiently to be paroled from the hospital at the same time that 9 of 24 patients who were operated on were paroled. Later reports showed that 7 of the control group and 8 of the group operated on were out of the hospital. Also, necropsy that failed to show any significant lesion in the brain of a recovered patient who had presumably undergone lobotomy has been reported.

On the basis of my earlier critical review, it was suggested that the field of psychiatry might profit by adopting the suggestion of Penrose, namely, that reports of the outcome of therapy be withheld until five years have elapsed after termination of treatment. This technique has been adopted with success by surgeons and radiologists in judging the therapeutic effectiveness of treatment for malignant processes.

In the past five years data have accumulated that allow a much better appraisal of the value of prefrontal lobotomy. Many of the questions unanswered in 1947 have now been clarified, although new problems have arisen through the application of such modified techniques as transorbital lobotomy, topectomy, thalamotomy, undercutting of the cortex, and anterior cingulectomy. Since these procedures have not been used over a sufficient period to allow satisfactory evaluation of their therapeutic potentialities, it has been decided to avoid discus-

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sion of them at this time. The intent is, rather, to examine and discuss the indications for lobotomy, the available knowledge of its usefulness, and the known common complications of the procedure.

INDICATIONS FOR LOBOTOMY

Lobotomy has been recommended extensively in the treatment of the hospitalized psychotic patient, with the ultimate aim of effecting a social recovery outside the hospital. It also is used for the control of the dangerously suicidal, assaultive, or destructive patient in whom social recovery is unlikely. The procedure has been done on overactive psychotic patients who have physical disease, such as tuberculosis, that may be seriously influenced by the behavioral abnormality. It has been applied in the treatment of the ambulatory, nonhospitalized, psychotic patient and various types of neurosis. It has been used for psychopathic states, drug addiction, organic behavioral disturbances, and intractable pain of physical or psychic cause. It is generally recognized that lobotomy provides only modification of certain symptoms. It is not a specific therapy in any sense. This is clearly demonstrated in such reports as those of McLardy and Davies, who have found that relapse may occur, with recurrence of all symptoms noted preoperatively, even when as extensive a procedure as bilateral prefrontal lobectomy is performed.

There seems to be fairly general agreement that certain specific symptoms are more likely than others to be modified by lobotomy. Suicidal tendencies, refusal of food, depression, anxiety, hypochondriasis, assaultiveness, destructiveness, impulsiveness, and overactivity are likely to be influenced favorably by lobotomy in more than 75% of the cases. Delusions and hallucinations are less likely to be modified, although the patient does not respond with as great emotion to the disordered thought process. Apathy, indifference, withdrawal, untidiness, or inappropriate emotional responses of long standing are behavioral patterns that are seldom modifiable by this procedure and are considered by some as contraindications for the operation. Certain features suggest a favorable outcome from lobotomy for the illnesses of certain hospitalized psychotic patients. These are sudden onset of illness, short duration of symptoms, a good prepsychotic personality, and plasticity of symptoms; however, experienced psychiatrists have long been aware that these factors indicate a favorable outcome even with conservative treatment.

There is, at present, a growing insistence by some that lobotomy be performed as early as possible in order that patients may obtain the benefit of the operation before symptoms become fixed. It is true that few patients with chronic psychotic processes respond, and the hopes of therapeutic success in such patients frequently are not realized. There seems little justification at this time for supporting the contention of those who press for early operation. The reason for this point of view is easily demonstrated. Penrose, in his study of outcome of various therapeutic methods used in the public mental hospitals of Ontario, Canada, over a five year period, found that at the end of one year about 50% of the hospitalized, psychotic patients who were not treated by shock had been discharged from the hospitals. At the end of two years this figure was almost 60%. Few discharges took place in this group after the end of the second year. There is, at present, no way of selecting the 60% of psychotic patients who will recover with conservative care during the first two years of hospitalization. Those who advocate lobotomy prior to the end of the second year of hospitalization have not had sufficient experience to justify the use of the procedure on the 6 of 10 patients who will recover sufficiently without operation. Those who contend that lobotomy is often delayed too long do, however, have a point. Several excellent follow-up studies indicate that patients who have been hospitalized for more than five years are unlikely to receive much benefit from the procedure, although in some instances behavior in the hospital may be more circumspect after operation.

Lobotomy seems to offer a better opportunity for increasing the rate of discharge of patients hospitalized for more than two years. This fact is attested by several recent reports. That from Pilgrim State Hospital, New York, by Worthing and his associates, showed that a 10% release rate continues into the 12th year of hospital life when lobotomy is used. Yet, the quality of remission is much less satisfactory in patients operated on late in the course of their illness.

SELECTION OF PATIENTS

The following factors must be considered in selection of patients for lobotomy. A major factor working against the social reintegration of the patient who has had a lobotomy, as with any mental patient, is the attitude of the family or those on whom he is dependent. This factor has been commented on by many. The willingness of the family to accept, support, and direct the rehabilitation of the patient who has undergone lobotomy and shows the exaggerated dependence so commonly the result of the brain lesion is of such importance that the Greystone Park investigators of topectomy had their social workers develop a rating scale to evaluate the responsibility of the family for their relatives. Interviews with the family to explain the personality changes that occur after lobotomy are recognized as a necessity to effect a favorable extrahospital outcome. The failure of the family to adjust to the returned patient often results in his readmission to the hospital. In some instances, this failure is due to the continuing existence of the psychosis or to appearance of symptoms secondary to the frontal lobe lesion indicative of social irresponsibility that few families can tolerate.

The varying effects of the return of such patients to their families have been described in several articles. Partridge reported on the rehabilitation of a family following operation on the psychotic member. Koskoff, on the other hand, indicated that a family's equilibrium was disturbed by the changed behavior of a wife who was successfully relieved of a chronically painful condition by prefrontal lobotomy. The anxiety caused by her outspoken and unpleasant postoperative behavior induced disturbances in her husband and daughter that led to their respective breakdowns with a gastric ulcer and schizophrenia. The difficulties of family acceptance of the patient treated by lobotomy have been discussed also by various social agencies.

Probably the most important single factor in selection of a patient for lobotomy is evidence that he is responding emotionally to his environment. Patients who offer a series of desperate complaints, who are aggressive, anxious, or restless, or who betray evidence of disturbed autonomic functions, such as large pupils, dry tongue, tachycardia, or cold, moist hands, are more likely to benefit than those who are withdrawn, apathetic, and dull. Certain rating scales of behavior have been devised in an attempt to estimate the patient's potential for recovery.

Another matter of prime importance that must be considered before the decision to operate is made is the occupational status of the patient prior to the onset of his illness. It has been the common experience that those who are employed in simple occupations are more likely than others to return to a similar form of work after lobotomy. Freeman and Watts early stated that no physician, dentist, artist, musician, or writer had resumed his profession after lobotomy. The inability of those whose skills demand a high degree of social adaptability, tact, and creativeness to return to their chosen work is probably the result of the deficit induced by the frontal lobe lesion. In the past few years, the return of a few nurses and physicians to gainful employment after lobotomy has been reported, but whether the level of their activity is as high as that prior to operation is not easy to ascertain. It is a serious matter, indeed, to recommend frontal lobotomy as treatment for anyone with particular social or creative talent if there is any hope of recovery through more conservative measures.

The age, sex, religion, and education of the patient have not been found to have major significance in the selection of patients for operation, although the existence of cerebral degenerative processes in the elderly patient suggests a poor outcome. It is of interest that twice as many women as men have undergone this operation in the United States.

EFFECTIVENESS OF LOBOTOMY

When the effectiveness of lobotomy for treatment of specific reaction types is considered, there seems to be a general conviction that the procedure is of most value in the treatment of the less disruptive personality disorders, such as obsessive and compulsive states, certain hypochondriacal reactions, and the involutional depressions. Manic-depressive psychoses respond more favorably than do schizophrenic reactions; however, a study of the number of patients operated on in each category compiled from seven recent reports with follow-up investigations showed that about 60% of the patients had schizophrenia, 25% had affective psychosis including the involutional states, 10% or less had obsessive, compulsive neurosis, and the remainder had scattered conditions, including psychoneurosis, psychosomatic conditions, psychopathic states, organic psychoses, mental defects, epilepsy, and painful conditions.

Prefrontal lobotomy has not been shown effective in relieving schizophrenia. Experience makes it clear that it offers little to the vast majority of patients who form the bulk of the patient load in our mental institutions. This is due to the fact that most of them fail to have the symptoms, previously mentioned, that are generally affected by the procedure. Yet the procedure has led to the return to the community of a number of schizophrenic patients who had been hospitalized for two or more years and who were unlikely candidates for discharge. Furthermore, it is generally agreed that the use of lobotomy in chronically disturbed and destructive patients often has led to subsidence of such behavior. Such symptomatic modification has eased the burden of hospital management, even though social readjustment with discharge has not always ensued. The suggestion that our state institutions will be emptied by the use of the procedure should, however, be considered an expectation that cannot be fulfilled.

Opinions differ with regard to the type of schizophrenic reaction most likely to be benefited by the operation. Some state that the periodic catatonic type responds best and that the hebephrenic, paranoid, and simple reaction types respond less well in the order mentioned. Others have reported better success with hebephrenic and paranoid reactions. This difference in opinion is perhaps due to the well-known variations in diagnostic criteria for schizophrenia and its subgroups from one hospital to another and the fact that patients with this illness may manifest from one time to another during its course catatonic, hebephrenic, or paranoid symptoms.

The quality of the improvement obtained by prefrontal lobotomy is best illustrated in the follow-up study by Partridge, who personally reexamined 158 schizophrenic patients treated by psychosurgery. Of 74 patients initially discharged from the hospital, 16 were still psychotic at time of dismissal, 2 of whom had relapses; 16 showed psychotic traces at time of dismissal, 2 of whom had relapses. Thirty-six were discharged as recovered; 7 of these had relapses and 4 recovered after the relapse. Six psychotic patients were discharged against advice. In other words, while 46.8% were discharged from the hospital, many still manifested evidence of the psychotic process. The eventual adjustment of such dischargees is worthy of further study at a later date. A number will be returned to the hospital when their dependent needs cannot be met by their families and the community. It is of interest that of the original 19 schizophrenic patients operated on under the direction of Moniz, only 3 were well 12 years later; initially, 5 were discharged in remission.

While five years ago relatively few patients who had manic-depressive psychoses had been treated by psychosurgery and followed for any period, now a significant number have been observed. The extremely variable course of this illness makes any evaluation most insecure. Certain impressions are available, however. The outcome is more satisfactory among patients with predominantly depressive illness in whom the duration of the attacks is reduced, their severity mitigated, and periodic recurrence fragmented. The existence of manic features is an ominous sign so far as expectation for social recovery is concerned. The poor outlook for the elated patient is not modified whether the surgical procedure is performed during or between manic phases. The procedure does not fully control either phase of the manic-depressive psychosis, but manic behavior is less commonly modified. Furthermore, patients with manic-depressive psychosis who have aggressive thoughts prior to lobotomy are likely

to have frank antisocial behavior following it. In Stengel's study, only 5 of 75 patients failed to reveal features of a frontal lobe syndrome after operation. To many, the personality distortion caused by this syndrome is not considered of major significance in comparison to the gross symptoms of the illness for which the operation is performed.

The so-called involutional psychoses have responded well to prefrontal lobotomy. Of 273 patients treated by five different groups, 61% were able to leave the hospital. The obsessive-compulsive neurosis also responds to prefrontal lobotomy. Some patients have been reported relieved of their obsessive thoughts and compulsive behavior after operation, while others maintain their symptoms but no longer are so driven by them. Occasionally persons with obsessive-compulsive neurosis may become aggressive after lobotomy and exhibit the behavior pattern reminiscent of the antisocial psychopath. Patients with this neurosis, when treated by psychoanalytic methods, show a rate of improvement equally as impressive as that from lobotomy. If psychoanalysis is practicable, it should be advised before lobotomy is considered. Psychoanalysis by its nature is limited to patients who are reasonably intelligent, who are within rather narrow age limits, and who live in areas in which this therapy is available. Lobotomy may be considered when psychoanalysis has proved ineffective or when this treatment is not available. Lobotomy is a doubtful procedure in the treatment of obsessive-compulsive neurosis in which the person is capable of an active and productive social and occupational life.

In general, the treatment of the antisocial or sexual psychopath has not been successful. On the other hand, there have been reports of modification of deviant antisocial or sexual behavior. The probable explanation for the differing response may lie in the force motivating the type of behavior. In the psychopath whose deviant behavior is an expression of failure to develop a good conscience, the frontal deficit produced by operation, which usually lowers inhibitions, only leads to exaggeration of previous unfavorable behavior traits. On the other hand, when antisocial behavior is an expression of a compulsive drive arising as a substitution for some deep-seated unconscious conflict, the surgical procedure may lead to a lessening of this drive and, therefore, of the aberrant behavior trait. It is possible that better selection of patients on the basis of the psychic causation of their behavior may lead to a more successful, though circumscribed, range of usefulness of lobotomy in treatment of those with antisocial behavior.

The question has been raised as to whether lobotomy leads to deviant sexual activity in patients who had not displayed sexual abnormalities before. The eruption of homosexual behavior in both men and women has been observed following prefrontal lobotomy. Exhibitionism occurred in several patients after operation, and pedophilia occurred in another. It is not clear whether these patients expressed their aberrant sexual drives prior to operation or whether they became evident first in the postoperative period.

In a detailed study of sexual activity in 40 patients Levine and Albert found that 4 showed aberrant sexual behavior in the postoperative period that involved them in social difficulties. One, a sexual psychopath before the onset of psychosis, returned to promiscuous behavior after operation. Another who had not been a social problem before operation became one. Two other patients who remained psychotic were in constant difficulty owing to their sexual verbalizations. In their series, homosexuality "did not arise anew" after operation. Levine and Albert concluded "that the predominant prelobotomy mode of sexual activity was maintained after lobotomy."

The successful treatment of patients with persistent pain by transection of the thalamofrontal radiations is probably the most significant new contribution to medical knowledge that has evolved from lobotomy. The observation that such patients no longer complain of pain although they retain their ability to perceive painful stimuli has emphasized the complexity of the problems of pain. Freeman has stated that few patients relieved of unbearable pain of organic disease have made good social adjustments following lobotomy. The procedure has been used with success to relieve the intractable pain of carcinoma, the thalamic syndrome, neurological states including tabes dorsalis, and the painful phantom. Unilateral lobotomy is often successful in the treatment of such conditions. Unilateral lobotomy has failed in patients who, in addition to having a known organic cause for their symptoms, also show evidence of a psychogenic disturbance. Yet, bilateral lobotomy succeeded in relieving pain in most patients in whom both physical and emotional factors contributed to the painful symptom. It is my impression that the decision to employ this procedure or the decision to undertake initially a unilateral or bilateral operation should not be made in any case until careful psychiatric evaluation has been carried out. Furthermore, such an evaluation should be made of any patient with a chronic painful condition before any neurosurgical procedure is undertaken. In some instances in which the pain is primarily caused by a physical lesion, lobotomy is initially preferable to chordotomy or neurectomy. In other instances, the opposite conclusion may be drawn as the result of a good neuropsychiatric study.

Prefrontal lobotomy is an effective form of treatment for patients whose painful complaint represents a part of a severe obsessive-compulsive neurosis or a psychotic state when these conditions have proved refractory to other forms of treatment, such as psychotherapy or electroshock therapy. In general, its use seems inadvisable for patients with hysterical or traumatic neurosis whose painful symptoms are frequently intermittent and seldom entirely incompatible with a reasonable social adjustment. The procedure is not to be recommended for psychoneurotic depressive states or obsessive states associated with pain and even addiction when the patient is found to be carrying important responsibility in business or at home. It is dubious whether it should be used when the patient with pain is managing successfully outside the hospital but is isolated, without relatives or friends, since the operative procedure may lead to such a severe reduction in productive capacity and such an increase in dependence that institutionalization may become necessary.

Procaine hydrochloride block of the frontal poles through a transorbital wound has been of aid in the selection of patients for whom prefrontal lobotomy may be indicated to relieve intractable pain. With relief of pain by prefrontal lobotomy it has been possible to withdraw narcotic drugs from patients addicted to them, provided this measure was instituted immediately after operation. Careful studies have shown that the symptoms of physiological dependence on narcotics, known as the abstinence syndrome, do occur when withdrawal of the narcotic is performed, although they are somewhat less intense in the immediate postlobotomy period. This is a matter of some importance. Sudden withdrawal of narcotics in a person strongly addicted may lead to serious abstinence symptoms in the postoperative state, which could be overlooked owing to the patient's failure to complain. At present there is no satisfactory means of assessing the value of prefrontal lobotomy in the treatment of other neuroses. Suffice it to say that satisfactory outcome may result from more conservative intervention.

RESULTANT COMPLICATIONS

The major complications that result from prefrontal lobotomy are as follows: the frontal lobe syndrome, convulsive disorders, urinary disturbances, certain surgical complications, and even death. The general practitioner may be called on to provide advice in regard to the indications and limitations of the procedure as well as to diagnose and manage these complications. It has been stated that lesions of the frontal lobe accentuate the basic features of the individual personality. Thus, patients who have been shy and withdrawn most of their lives may become more socially aloof. Persons with a personality leaning toward hypomania may show increased aggressiveness. The person who had a satisfactory social adjustment in the prepsychotic state is most likely to make the best adjustment after operation.

The most conspicuous and most disturbing deficit that has been observed as the result of prefrontal lobotomy is that best perceived by the patient's close relatives or friends and manifests itself in the patient's social behavior. Lack of tact is a frequent postoperative phenomenon, and the various uncouth, blunt, or facetious remarks made by the patient may become a source of embarrassment to the family. The patient's sense of personal responsibility for social behavior is lowered. Some degree of emotional dulling takes place. Judgment suffers considerably. The patient may no longer consider a group of related factors and come to a well-thought-out conclusion. Abstract reasoning and the ability to synthesize are impaired. Ability to plan activity beyond simple habitual routine suffers. Initiative is depressed.

The mortality rate from the operative procedure has varied from 3 to 6%. Postoperative convulsive disorders occur in 3 to 12% of patients. If a second lobotomy is performed, the incidence of convulsions is increased. Causes of death have been cerebral hemorrhage (especially from the anterior cerebral artery), abscess, meningitis, atelectasis, and pneumonia. The acute complications are generally recognized and treated during hospitalization. Occasionally, the physician may be called on to recognize a subdural hematoma or a brain abscess that may have become manifest some time after the operation. The symptoms of these conditions are the same as those when the lesions are due to other causes. The postoperative management of convulsions may be necessary.

Although the family physician may have little to do with the immediate postoperative care of the patient who has had a lobotomy, he may be responsible for long-term home care. He may be required to decide what measures should be taken in regard to the unusual behavior of the patient that has become embarrassing to the family. The patient's disturbance may, for example, become manifest in some socially unacceptable behavior, or he may be considered "dangerous" to the community for one or another reason. If there is grave cause for alarm or if the family is unwilling to accept responsibility, institutional care is indicated. The recurrence of the original psychotic symptoms is also an indication for advising this step.

The question of the daily program of activity needed to aid in the patient's readjustment may be presented for consideration. A comprehensive, yet stimulating schedule of daily activities has been found to assist the readjustment process. Such a schedule includes regular hours for meals, set personal and household routines, physical activity, recreational pursuit, work, hobbies, and even simple habit retraining for patients who exhibit difficulty in managing their toilet and bathroom habits. Return to his occupation may be attempted after a satisfactory home adjustment has been made. Few who have not returned to work within a year are likely to be profitably employed. Some of these may, however, be able to contribute productively in a less demanding occupation or by assisting with housework at home. Often a simple explanation to a prospective employer by the physician will do much toward obtaining a satisfactory job adjustment.

SUMMARY

Prefrontal lobotomy has proved, over 15 years' experience, to be a useful therapeutic procedure in the treatment of certain emotional disorders and cases of intractable pain. It is symptomatic therapy that has proved most effective in relieving destructive drives, chronic depression and obsessions, hypochondriasis, impulsiveness, and overactivity. It seems to promise return to the community of a greater number of patients with chronic mental disease who have been hospitalized for more than two years than does any other therapeutic procedure. Relapse, with full recurrence of the symptoms of the original mental illness, may occur after prefrontal lobotomy. There is evidence that patients who have undergone lobotomy are more sensitive to environmental stress after operation than before. While most patients show evidence of deficit due to the lesion of the frontal lobe, this defect often is not as disturbing as the emotional illness they had. Other complications frequently encountered are convulsions and urinary incontinence and urgency. The general practitioner may be called on to advise the family in regard to the indications for operation and the limitations and complications of the procedure. He may also assume active responsibility for care of such complications and assist the family in the rehabilitation of the patient at home and in the community.

CORONARY DISEASE AMONG UNITED STATES SOLDIERS KILLED IN ACTION IN KOREA

PRELIMINARY REPORT

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The purpose of this paper is to describe and analyze the gross lesions found in the coronary arteries of United States soldiers killed in action in Korea. The histology will be discussed in detail in a subsequent paper as will such pertinent data as race, body build, and personal habits.

MATERIAL

Recently 300 autopsies were performed on United States battle casualties in Korea. Most of these soldiers were killed in action or suffered accidental death in front line areas. The coronary arteries were carefully dissected in all cases. No case in which there was known clinical evidence of coronary disease was included in this series.

The average age in 200 cases was 22.1 years. The ages in the first 98 cases were not recorded except that the oldest patient was 33. In the entire series, the youngest recorded age was 18 and the oldest 48.

FINDINGS

In 77.3% of the hearts, some gross evidence of coronary arteriosclerosis was found. The disease process varied from "fibrous" thickening to large atheromatous plaques causing complete occlusion of one or more of the major vessels (table 1).

Occlusion was considered complete only when the plaque had no free surface and was fused to the wall opposite its point of origin. A conservative attitude in estimating the amount of luminal narrowing was maintained throughout. No actual measurements were made.

TABLE 1.—*Percentage of Cases Showing Varying Amounts of Luminal Narrowing*

Amount of Luminal Narrowing	% of Cases
"Fibrous" thickening or streaking causing insignificant luminal narrowing	35.0
Plaques causing luminal narrowing over	
10%	13.3
20%	6.3
30%	3.7
40%	3.0
50%	3.0
60%	1.7
70%	1.0
80%	1.3
90%	5.3
Plaques causing complete occlusion of one or more vessels	3.0

In several of the cases listed in table 1 as showing over 90% luminal narrowing, the plaques completely filled the lumen but displayed a free surface not fused with the intima. Hypertrophy was not observed in any heart examined. The size could not be correlated with the severity of disease found in the coronary arteries.

From the Armed Forces Institute of Pathology, Washington, D. C.

In the great majority of cases, the location of the lesions followed a constant pattern. If the lesion was found in the proximal third of the left coronary artery, it was usually thickest on the epicardial side of the lumen, whereas, if it was in the distal third of the artery just proximal to the bifurcation of the circumflex artery, it tended to assume a more medial position. At the bifurcation, the plaque was constantly found on the wall of the left coronary artery directly opposite the ostium of the circumflex artery (fig. 1). In the upper fourth of the anterior descending artery, the disease process was usually found on the medial posterior wall of the vessel. More distally, the posterior or myocardial side of the lumen was the common location (fig. 2*A*). The medial branch of a bifurcating anterior descending artery was always more severely involved in cases showing extensive disease (fig. 2*B*). In some cases, plaques were encountered on the epicardial side of the lumen of the anterior descending artery; these plaques were opposite the bifurcation of a septal branch.

TABLE 2.—*Sites of Lesions Found in Coronary Arteries at Autopsy*

Site	No. of Cases
Left coronary	
Above bifurcation	10
At bifurcation	22
And circumflex	1
And right coronary	1
Circumflex, and right coronary	1
Anterior descending	
Branch	114
And circumflex	13
And right coronary	33
And left coronary	5
Left and right coronaries	4
Left coronary, and circumflex	1
Circumflex, and right coronary	8
Left and right coronary, and circumflex	11
Right coronary only	3
Circumflex only	4

The pattern of disease was not as constant in the circumflex artery as it was in the left and anterior descending branches. Streaking and/or plaque formation was oftenest observed on the superior and posterior walls of the proximal fourth of the vessel, while the next most frequent site of involvement was the posterior wall in the middle third of the vessel, usually opposite a bifurcation of the circumflex artery.

In the proximal fourth of the right coronary artery, small plaques were commonly encountered on the posterior wall opposite the adipose branches. Elsewhere in the right coronary, plaques were usually found on the posterior and superior walls. This was especially true at

the right border of the heart opposite the origin of the right marginal artery.

Disease was most commonly found at the bifurcation of the circumflex artery and in the 3 cm. of anterior descending artery distal to the bifurcation (table 2). In 54 of the 112 cases with lesions in the anterior descending

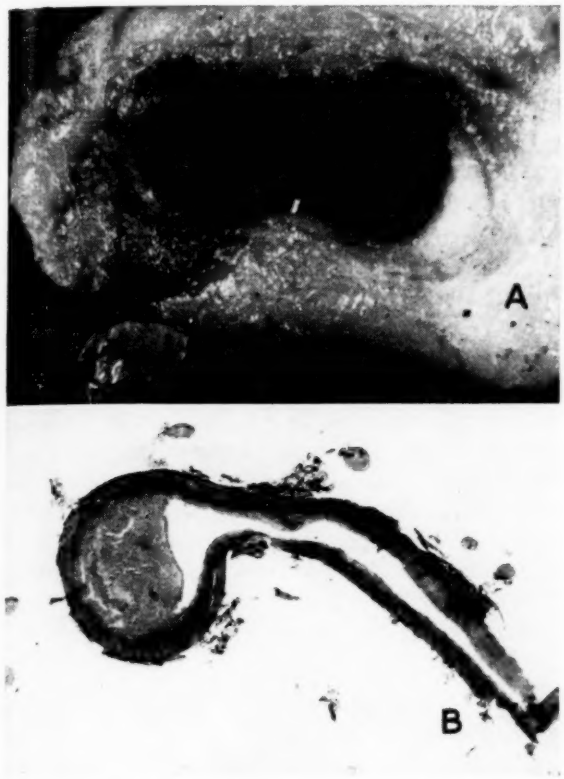

Fig. 1.—*A*, plaque formation in left coronary artery opposite ostium of circumflex (× 4). *B*, detail of atheromatous plaque shown in *A* (× 14).

artery, the disease process started at the bifurcation of the circumflex artery and extended down the anterior descending branch, usually on the medial and posterior sides of the lumen. In every instance in which the diseased anterior descending artery bifurcated in the first 2 cm., the deposition of atheromatous material appeared to be intensified. The angle formed by the anterior descending and circumflex arteries is important. An angle approaching 80 degrees always seemed to predispose the artery to the development of a plaque. On the other hand, the disease process tended to be modified when the circumflex artery arose at the ostium of the right coronary artery, the vessel coursing around the base of the aortic and pulmonary arteries to assume its usual position in the atrioventricular septum on the anterior surface of the heart. Minimal disease was found in the left coronary artery in three such cases.

COMMENT

It is apparent that the lesions are commonly located at or near points of bifurcation; this gives the impression that hemodynamics in the lumen about bifurcations must play an important part in the mechanism of plaque formation.

The phasic aspect of the coronary circulation is mainly the result of the aortic blood pressure and the contractions of the myocardium during the cardiac cycle. Gregg and Green [1] have shown experimentally that, during isometric contractions and ejection, the blood in the deeper and more strongly compressed vessels in the myocardium is forced backward into the larger proximal channels. Wood [2] stated that, during systole, ventricular contractions prevent blood from flowing through the coronary vessels that penetrate the left ventricular muscles, while the larger arteries on the surface dilate to form an elastic reservoir that recoils during diastole and acts as an accessory pump forcing the blood onward. During ventricular relaxation, the blood is able to flow through the vessels penetrating muscle, because it is propelled by the aortic diastolic pressure and by the recoil of the elastic reservoir. The compression of the intramural arteries is, as noted by Friedberg,[3] less in the right ventricle.

We maintain that eddying about bifurcations of the coronary arteries, occurring during the diastolic recoil of the dilated coronary arteries, is a dynamic factor in the mechanism of plaque formation. As has been shown, the most frequent sites of plaque formation are on the medial wall of the left coronary artery at the bifurcation of the circumflex artery and on the medial and posterior sides of the proximal fourth of the anterior descending artery. The severest disease was found in those cases in which the bifurcation of the circumflex artery formed an 80 degree angle and the anterior descending artery gave rise to a large branch just distal to the origin of the circumflex artery. It is postulated that under such conditions

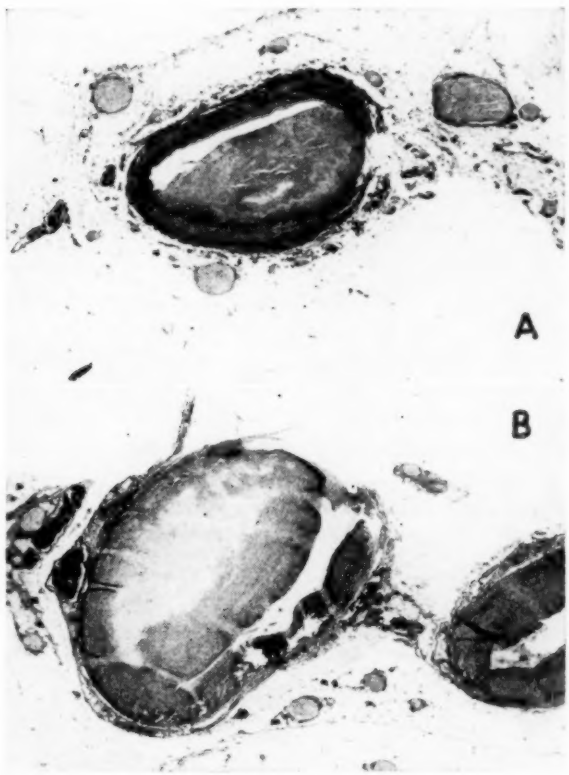

Fig. 2.—*A*, large plaque on myocardial side of anterior descending branch (× 12.5). *B*, large plaque in medial branch of a bifurcating anterior descending artery (× 18.5).

1. Gregg, D. E., and Green, H. D.: Registration and Interpretation of Normal Phasic Inflow into the Left Coronary Artery by an Improved Differential Manometric Method, Am. J. Physiol. **130**: 114-125, 1940.

2. Wood, P. H.: Diseases of the Heart and Circulation, London, Eyre & Spottiswoode, Ltd., 1950.

3. Friedberg, C. K.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1949.

eddying of blood in the left and anterior descending arteries traumatizes the intima and, thus, starts the vicious circle of plaque formation.

Many factors have been mentioned as the primary cause of coronary arteriosclerosis. Heredity has been accepted by many as an important agent in the development of coronary disease. This may be manifested in the inherited pattern of coronary artery distribution. It has long been realized that coronary artery disease is much commoner in young men than in young women [4]; this suggests a hormonal factor. Boas and Ludwig [5] have shown experimentally that testosterone stimulates the formation of connective tissue, while estrogens inhibit connective tissue formation. Some investigators have emphasized the ratio of serum cholesterol to phospholipids. According to Gofman and associates,[6] at any total serum cholesterol level, the S_f 12-20 and S_f 20-100 classes of lipoproteins are higher in patients with coronary disease than in normal subjects.[7] Winternitz, Thomas, and Le Compte [8] demonstrated with histological preparations and carefully executed reconstructions that intramural hemorrhage may furnish the bulk of cholesterol material in arteriosclerotic lesions, while Wartman and Laipply [9] produced intramural hematomas experimentally and caused sclerosis in 30% of their cases. Saphir and Gore [10] presented evidence of an inflammatory basis of arteriosclerosis.

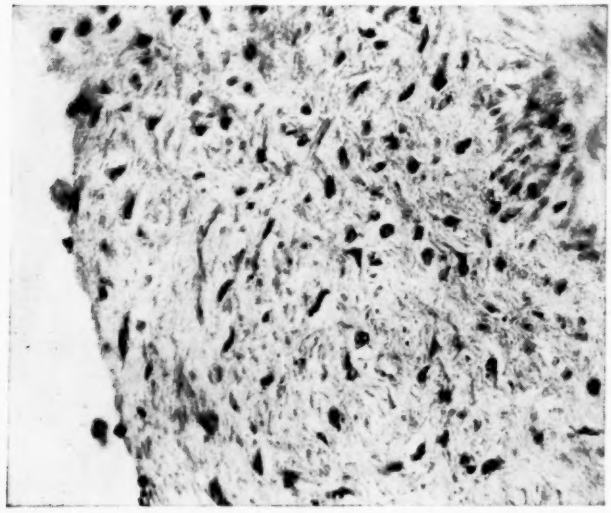

Fig. 3.—Thick intima in artery of a young Korean prisoner of war (× 33.5).

Of special interest is the work of Dock [11] in which he demonstrated that the coronary intima of the male newborn is thicker than the intima of the female newborn. Zink [12] and Lack [13] maintain that this phenomenon occurred only at points of bifurcation.

Most investigators are of the opinion that these areas of thickening are developmental irregularities representing prearteriosclerotic or early arteriosclerotic lesions.

It is interesting to note that the intima of the coronary vessels in young Koreans is thick (fig. 3), although coronary atheromatosis is said to be rare in that race. Here we have an anatomic feature indicating stress, but plaque formation is rare. This would strongly suggest dietary factors. It is most unlikely that one factor alone can be indicated as the cause of coronary sclerosis. The findings presented in this paper indicate wear and tear on the intima caused by eddying of blood at points of bifuration. However, other basic factors, such as hormones and diet, must be present before the disease progresses to plaque formation.

Two important points should be emphasized in view of observations made in this study. 1. Thrombosis occurs more commonly in diseased arteries, especially in cases in which extensive trauma and shock exerted their influence (fig. 4). 2. In cases of sudden or clinically unexplained death of young men, the presence of a completely occluded coronary artery is not necessarily the cause of death.

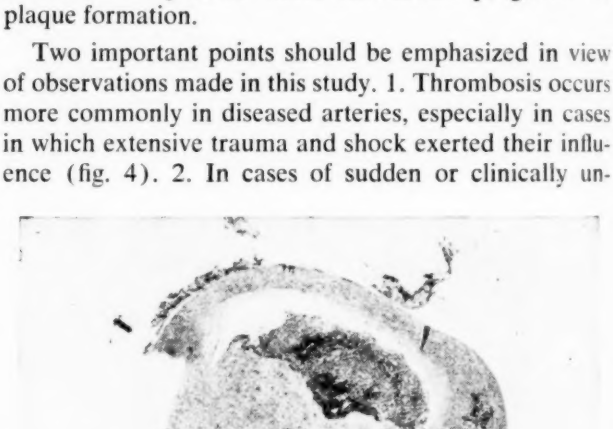

Fig. 4.—Thrombosis of anterior descending artery in a 21-year-old white man who died three days after severe injuries (× 21.5).

SUMMARY

The coronary arteries of 300 soldiers killed in action were dissected. The average age of the men in this group was approximately 22.1 years. In 77.3% of the cases,

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6. Gofman, J. W., and others: Atherosclerosis, Lipoproteins and Coronary Artery Disease, in Karsner, H. T., and Sanford, A. H.: Yearbook of Pathology and Clinical Pathology, Chicago, The Year Book Publishers, 1951, pp. 110-125.

7. S_f signifies Svedbergs of flotation.

8. Winternitz, M. C.; Thomas, R. M., and LeCompte, P. M.: The Biology of Arteriosclerosis, Springfield, Ill., Charles C Thomas, Publisher, 1938.

9. Wartman, W. B., and Laipply, T. C.: The Fate of Blood Injected into the Arterial Wall, Am. J. Path. **25**: 383-395, 1949.

10. Saphir, O., and Gore, I.: Evidence for an Inflammatory Basis of Coronary Arteriosclerosis in the Young, Arch. Path. **49**: 418-426 (April) 1950.

11. Dock, W.: The Predilection of Atherosclerosis for Coronary Arteries, J. A. M. A. **131**: 875-878 (July 13) 1946.

12. Zink, K. H.: Sondervorrichtungen an Kranzgefässen und ihre Beziehung zu Coronarinfarkt und miliaren Nekrosen, Virchows Arch. path. Anat. **305**: 288-297, 1939.

13. Lack, A. R.: The Coronary Arteries in the Newborn and Childhood, cited by Anderson, W. A. D.; Pathology, St. Louis, The C. V. Mosby Company, 1948, p. 559.

some gross evidence of coronary disease was demonstrated that varied from "fibrous" thickening to complete occlusion of one or more of the main branches. The exact locations of the lesions were shown to be at or near points of bifurcation of the vessels. The hemodynamics of the coronary circulation as modified by the anatomic variations of the coronary arterial tree are implicated as an important factor in the formation of plaques.

7th St. and Independence Ave. S. W., Washington 25, D. C. (Major Enos).

PRIMARY RESECTION OF THE COLON IN ACUTE ULCERATIVE COLITIS

Charles B. Ripstein, M.D., Brooklyn

Acute fulminating ulcerative colitis is a serious disease that carries a very high mortality. The acute attack may be an exacerbation of preexisting disease or it may represent the first manifestation of colitis in a previously apparently healthy person. In either case, the patient is acutely ill with high fever, diarrhea, bloody and purulent stools, and an overwhelming toxemia. There is often evidence of peritoneal irritation or frank peritonitis. Because these patients are so acutely ill, there has been a tendency to avoid surgical treatment, and, when it has become inevitable, simple ileostomy has been accepted as the operation of choice.[1] The results of this therapy have been poor, and the mortality has ranged from 20 to 60% in reported series of cases. In analyzing the deaths that have occurred in the past, certain facts become apparent: 1. The majority of patients show evidence of severe blood and protein loss, and this continues even in the presence of a functioning ileostomy. The blood loss may amount to 200 to 300 cc. and the protein loss to 150 to 200 gm. in 24 hours. The source of this loss is the diseased colon, and replacement in a severely ill patient is difficult and at times impossible. Ileostomy adds the factor of fluid and electrolyte loss. 2. Infection is an important factor in mortality. Sepsis and toxic absorption are universally present, and perforation of the colon is common (it occurred in 20% of fatal cases). The source of infection is primarily the diseased colon (fig. 1).

Since all of these factors are derived from the diseased bowel, the logical solution would be its removal, and, since primary resection of the colon is so well tolerated in debilitated patients with chronic ulcerative colitis,[2] it has appeared worth while to evaluate the use of this procedure in acute fulminating cases of the disease. My experience with primary colectomy now covers 120 cases of ulcerative colitis, and in this group there have been five operative deaths. Forty-three of these cases fall into the acute category, and it is this group I wish to consider in detail.

INDICATIONS FOR SURGERY

Since acute ulcerative colitis responds to medical therapy in many cases, it is obvious that any radical surgical procedure should be reserved for cases in which it fails. This fact has led to the attitude that surgery is indicated only as a last desperate measure, and patients are referred for surgery in moribund condition. In an attempt to avoid this, I have adopted the following indications for surgical treatment. 1. The first is failure of medical therapy to produce a remission within a three week period. This period is arbitrarily chosen, but it has been my experience that if a patient does not begin to improve within three weeks, further delay is dangerous. During this interval, patients have been treated with transfusions, antibiotics, corticotropin (ACTH), methantheline (Banthine), and, in some instances, psychotherapy. Sixty per cent of the patients have responded to this treatment, and the other 40% have undergone surgical treatment. 2. The second indication is perforation, actual or impending. In the presence of frank peritonitis or free gas in the peritoneal cavity, surgical intervention becomes an emergency matter. In any patient in whom localized abdominal tenderness develops, impending perforation is suspected, and in these instances a plain roentgenogram of the abdomen often shows a markedly distended colon, with little or no evidence of small bowel dilatation. I have considered these findings an urgent indication for operation. 3. The third indication is the occurrence of continued or repeated bleeding, especially if hemorrhage is extensive enough to produce a shock state. This constitutes an urgent indication for surgical intervention. 4. The fourth indication is the presence of septicemia or metastatic infection, such as endocarditis, pyoderma, or arthritis, which must be treated by removal of the primary focus after administration of a preliminary course of antibiotics.

OPERATIVE TECHNIQUE

The technique of operation is simple and has become standardized. A left rectus incision facilitates mobilization of the splenic flexure and leaves the right side of the abdomen free for ileostomy. The colon is mobilized by freeing its lateral peritoneal attachments and detaching the greater omentum from the stomach. The mesenteric vessels are then ligated and divided, and the colon is removed to the level of the rectosigmoid. The terminal ileum is brought out through a stab wound in the right lower quadrant as a permanent ileac stoma. After the occurrence of two near fatalities from ascending ileitis, I adopted Dennis'[3] suggestion of doing frozen section biopsies of the terminal ileum and resecting enough so that the exteriorized bowel is microscopically free from disease. The divided rectosigmoid is exteriorized

From the Department of Surgery, Maimonides Hospital, and the State University of New York College of Medicine, New York.

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3. Dennis, C.: Ileostomy and Colectomy in Chronic Ulcerative Colitis, Surgery **18**: 435, 1945.

through a stab wound in the left lower quadrant. I feel that the principle of exteriorization of all diseased bowel must be strictly adhered to to avoid leakage and peritonitis.

The small segment of rectum is left in place, because I have felt that its removal would be too great a shock in

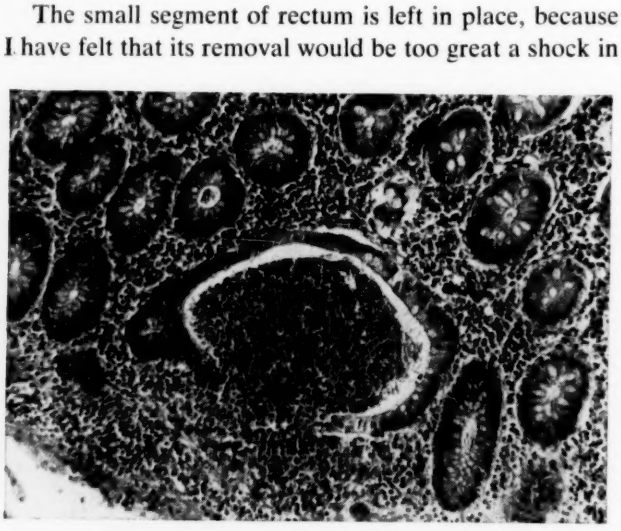

Fig. 1.—Microabscess in the submucosa of the colon in acute ulcerative colitis; these abscesses represent the source of infection and toxemia.

the poor risk patient. I have carried out a total colectomy in four patients in the chronic group but in none of the acutely ill patients. I have become convinced that a permanent ileac stoma is the price that must be paid for freedom from ulcerative colitis and that the rectal segment should be removed three to six months after the initial operation. It rarely heals after ileostomy and often gives rise to troublesome symptoms, such as bleeding, discharge, and fistula formation. In two cases, carcinoma has developed in the rectal segment. In four patients I have later anastomosed the ileum to the rectum, and in

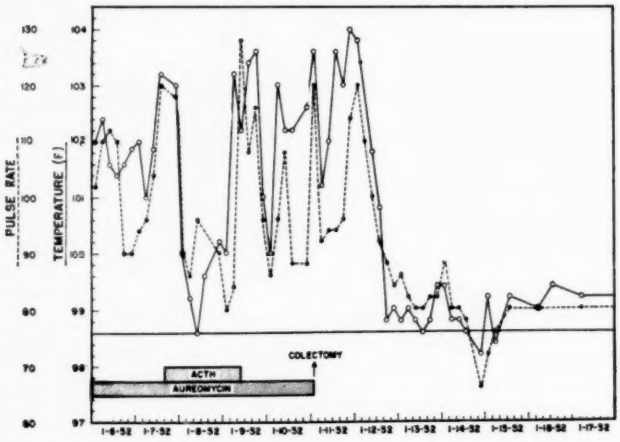

Fig. 2 (case 1).—Course of patient J. N., showing the response to resection of the colon.

three of these a recurrence of disease in the remaining colon has ensued. Two attempts at anal ileostomy have been failures because of severe excoriation of the anus, and I now feel that abdominal ileostomy, with use of the Rutzen bag, offers the most satisfactory solution for these patients.

RESULTS OF PRIMARY RESECTION OF THE COLON

In the past five years, one stage resection of the colon to the level of the rectosigmoid has been carried out in 43 patients with acute ulcerative colitis. All were in a toxic state, with severe diarrhea and fever of 103 to 105 F. In six patients, massive hemorrhage was a complicating factor, in eight perforation had occurred, and in three there was evidence of metastatic infection. Two cases were complicated by carcinoma of the colon. In all, medical therapy, including use of antibiotics, methantheline, and corticotropin had failed in a three week trial, or complications had ensued that necessitated emergency treatment. Two deaths occurred, one owing to ulcerative

Fig. 3.—The resected colon in case 1; this represents the length of bowel removed in the average case. The inflammatory process extends to the ileocecal valve.

endocarditis and septicemia in a patient who was moribund at the time of transfer to the surgical service and one postoperatively owing to peritonitis and intestinal obstruction. The remaining patients all recovered, one dying subsequently from carcinoma of the bowel. There were no deaths from ulcerative colitis on the medical service during this period. The following reports illustrate typical cases.

REPORT OF CASES

Case 1 (fig. 2).—J. N., a 30-year-old woman, was admitted to Maimonides Hospital Jan. 4, 1952, with a history of intermittent diarrhea for five years. She had noted acute, crampy abdominal pain, fever, and the presence of blood and pus in the stools for two days prior to admission. On admission she was dehydrated and in a toxic state, with a temperature of 104 F. The abdomen was slightly distended and tender, and sigmoidoscopic examination revealed an acutely hemorrhagic mucosa with many ulcerated areas. Despite aureomycin and methantheline therapy, the patient's course continued downhill. Corticotropin was given and produced a remission in the temperature, but the abdominal tenderness increased, and roent-

genograms showed a distended colon. Since there was no clinical improvement after three [illegible] of therapy and since the signs of peritonitis were increasing, colectomy was performed. The bowel was extensively involved with severe ulcerative colitis, with walled-off perforations in several areas (fig. 3). The postoperative course was uneventful, the temperature returning to normal within 36 hours and all toxic symptoms subsiding. This patient has continued to improve. She returned in three months for excision of the rectum because of local bleeding and fistula formation. Since that time she has led a normal life and has gained 40 lb. (18.1 kg.) in weight.

CASE 2 (fig. 4).—R. P., a 47-year-old woman, was admitted to Maimonides Hospital April 10, 1950, with a history of bloody diarrhea for three weeks and fever, weakness, and massive bleeding from the rectum for 10 days. On admission she appeared extremely ill and in a toxic state, with a fever spiking up to 103 F. Sigmoidoscopic examination revealed a fulminating, necrotic, ulcerative colitis with pseudopolyp formation. She was treated with transfusions and antibiotics, but her fever continued and the toxic state became severer. Bilateral pleuritis and pericarditis developed, and the abdomen became distended and tender. Because of her rapid downhill course and the development of obvious peritonitis, colectomy was undertaken April 14, 1950. At operation, the entire colon was extensively involved with ulcerative colitis, with three areas of free perforation and a walled-off abscess in the region of the splenic flexure. The colon was removed to the level of the lower sigmoid, which was exteriorized. The postoperative course was stormy, but the patient recovered and is alive and well today. She has had a subsequent abdominoperineal resection of the rectum because of continued bleeding and discharge.

CASE 3 (fig. 5).—W. J., a 29-year-old man, was admitted to Maimonides Hospital Sept. 19, 1951. This patient had had ulcerative colitis for 10 years, but 24 hours before admission he became acutely ill with severe abdominal pain, nausea, vomiting, and bloody diarrhea. At the time of admission, he was in an extremely toxic state, with a rigid, tender, distended abdomen. Roentgenograms revealed free gas in the peritoneal cavity, and a preoperative diagnosis of colonic perforation was made. Immediate laparotomy was performed, and at operation acute ulcerative colitis complicated by carcinoma

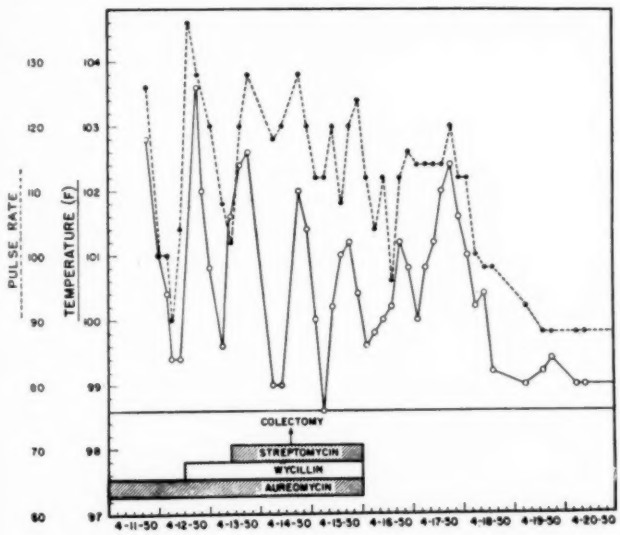

Fig. 4 (case 2).—Course of patient R. P., showing response to resection of the colon. (Wycillin is crystalline procaine penicillin G.)

of the transverse colon and a free perforation of the cecum was found. Colectomy and ileostomy were carried out, and the postoperative course was uneventful. The patient gained 40 lb. (18.1 kg.) in the next few months and was well for 10 months after operation, when he began to complain of back pain, which was found to be due to metastatic carcinoma.

COMMENT AND SUMMARY

It appears that primary resection of the diseased colon with ileostomy is the surgical procedure of choice in cases of acute ulcerative colitis that fail to respond to medical therapy. The operation may appear radical, but, in removing the source of blood and protein loss, elimi-

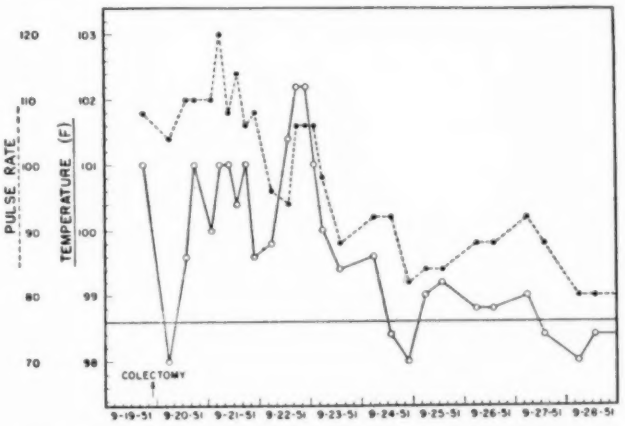

Fig. 5 (case 3).—Course of patient W. J., showing response to resection of the colon.

nating the focus of infection and toxic absorption, and forestalling the danger of perforation, it offers the patient a better chance of survival than does ileostomy alone. When ileostomy is performed without removal of the diseased bowel, the factors of fluid and electrolyte loss are added to the patient's burdens. An arbitrary interval of three weeks has been selected as the trial period for conservative management in these cases; if the patient does not improve in that time, operation is carried out. In the face of complications, such as hemorrhage or perforation, emergency surgery is indicated. The operation of primary colectomy was carried out in 43 patients with acute exacerbations of ulcerative colitis; there were two deaths in this group, a mortality of 4.6%.

4802 10th Ave. (19).

Diagnosis and Treatment.—It was a common reflection a couple of decades ago that treatment lagged behind diagnosis; the physician was often accused of being more interested in the latter than in the former. In so far as the charge had reference to the common bacterial infections the lag has been eliminated. Indeed, the position has perhaps been reversed. There is in this field such a wealth of available resources in treatment that the temptation to "get busy" with one or more of the "sulpha" drugs, or with one or other of the "antibiotics," or indeed, with one or other of both of these, before the nature of the infection is fully ascertained, is almost irresistible. This is not always the doctor's fault; his hand is sometimes forced by the patient's anxious friends, who do not know, as does the doctor, that powerful remedies sometimes have "side-effects," and that the patient's germ may have been rendered insensitive to the "antibiotic" when he badly needs it because he has already received it when it was not really necessary, or even indicated. But diagnosis is, after all, the alpha and omega of Medicine, and side by side with these slow advances in treatment came developments equally important, if less dramatic, in this sphere.—Lord Horder, M.D., Fifty Years of Medicine, *Journal of the Royal Institute of Public Health and Hygiene*, March, 1953.

MODERN EXTRAPLEURAL PNEUMOTHORAX IN THE CHANGING TREATMENT OF TUBERCULOSIS

J. W. Cutler, M.D., Philadelphia

Modern drug therapy and resectional surgery are producing dynamic changes in current thinking on the treatment of pulmonary tuberculosis. Pneumothorax, a long-established and flexible procedure, has been virtually abandoned in many institutions, because of possible complications, rather than limited to patients with proper indications. Thoracoplasty is decreasingly resorted to as an independent and definitive form of collapse. Extrapleural pneumothorax is seldom used because of prevailing prejudices. Pneumoperitoneum, an inefficient form of therapy and not without serious complications, is still popular in some quarters. On the other hand, resection is greatly on the increase and has become the treatment of choice with many physicians.

The development of streptomycin, *p*-aminosalicylic acid, and the isoniazid compounds has introduced new problems. Needed surgery is often delayed or neglected, with the hope that the new drugs will obviate all other therapeutic procedures. Overlooked is the fact that collapse or resection, or both, is ultimately needed in the great majority of cases to consolidate the gain achieved by bed rest and drug therapy, and the fact that surgery, if indicated at all, should be completed early in the course of therapy, when the tubercle bacillus is still sensitive to all the drugs. In the midst of such rapid and radical developments, the rules for good treatment in tuberculosis are still being formulated. Physicians, after all, are human beings too and, like other persons, are faddists to a considerable degree.

RESECTION

It is questionable whether the current marked trend to resection, on the assumption that resection is the best if not the only proper surgical approach, is really the best answer to the tuberculosis problem. It is possible to be overly enthusiastic about the newer benefits of resection and to forget the many valuable contributions good collapse therapy can make to recovery. This appears to be happening today. If the current trend is continued, a point is likely to be reached at which apparently little can be done for the tuberculous patient to assure recovery unless resection can be done, that is, unless the disease is sufficiently stabilized and localized for resection or can become so after months of bed rest and drug therapy and perhaps pneumoperitoneum. For the patient not so fortunate, this leads to a dreary, if not hopeless, outlook for a useful life, for he must depend solely on what drugs and institutional care can do for him. As a direct result of this trend, many patients are forced to stay in sanatoriums much longer than is really necessary or desirable, and the shortage of beds for tuberculous patients increases, although the death rate and incidence of the disease is dropping. This is an unsatisfactory and unhealthy situation and is really not an advance in therapy. On the contrary, it is a step backward, as the following recent case well illustrates.

CASE 1.—A white man, aged 35, married, consulted me on Feb. 2, 1953, and gave this history. He was first given a diagnosis of pulmonary tuberculosis on April 12, 1951, after a chest survey x-ray examination at his place of employment. There was moderately advanced disease, consisting largely of soft infiltration involving the middle two-thirds of the left lung field, with a small cavity in the outer zone of the second anterior interspace. There were also a few tuberculous deposits in the subclavicular area on the right. His general health was good, and for the most part he was asymptomatic. Tubercle bacilli were found in the sputum. On June 15, 1951, he was admitted to an institution, where he received rest, good food, all the antibacterial drugs available, a left temporary phrenic nerve interruption, and pneumoperitoneum. But his sputum continued to show tubercle bacilli, and on the whole the disease showed little resolution. The cavity remained open.

The patient, however, was getting restless. He was anxious to return home to a normal life and support his wife and child. In January, 1953, he asked his physician how much longer he would remain in the institution. He was told that at the rate his disease was improving it would take at least one more year before a limited resection could be undertaken and that another year of bed rest would be necessary after the operation to heal the diseased area that could not be removed by resection. He would have had three to four years of hospitalization, in other words, for a relatively mild case of moderately advanced tuberculosis, which before resection and chemotherapy could have been handled easily and effectively with therapeutic pneumothorax in a fraction of the time and at relatively little cost. As it was, intrapleural pneumothorax was not even suggested, let alone tried.

Resection and collapse, however, are not necessarily competitive or mutually exclusive procedures. On the contrary, they complement and supplement each other. But more important, they are needed in different types of patients. For instance, there are patients with special problems, such as a fibrotically stenosed bronchus, in whom collapse therapy is a predictable failure. In such instances resection is the answer. On the other hand, there are patients in whom the disease is so advanced and so badly distributed that resection cannot be considered at any time. In many such cases, collapse therapy has scored some of its most brilliant successes. Then again, collapse and resection have been combined successfully in the same patient. Both forms of therapy, resection and collapse, are valuable and necessary.

Most good results after resection are recorded in patients with roentgenographic evidence of limited or isolated and well-stabilized disease. But cases of such limited disease were never the real problem in tuberculosis therapy. It is the patient with the more advanced, more scattered, and less stabilized disease who constitutes the challenge and who represents the great majority of patients seeking treatment. For most of these patients reversible collapse, and not resection, is the better procedure. The problem, therefore, is a complex one, and it is important to keep an open mind. Obviously, integra-

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tion of therapy and careful planning of the over-all therapeutic attack to fit the needs of the individual patient are clearly indicated. Only in this way can the best interests of the patient be served. Such planning must also take into consideration the ultimate effect of the chosen therapy on pulmonary function, and all available methods of treatment should be employed, including, of course, collapse therapy. Important recent advances have taken place in this field, especially in extrapleural pneumothorax collapse, as well as in resection.

DEPRESSIVE EFFECT OF EXTRAPLEURAL COLLAPSE ON TUBERCLE BACILLUS

To fully appreciate extrapleural collapse, it is essential that one think of collapse therapy in terms of more than intensive rest. Important as this is, standing alone it fails to control the disease. Instead, one must think of collapse, first of all, in terms of a profound and long-continued depressive effect on the tubercle bacillus itself.

Extrapleural collapse deprives the bacillus (a strict aerobe) of vitally needed oxygen by preventing the normal replenishment of atmospheric air through closure of terminal bronchioles. This produces a specific inhibitory, even bactericidal, effect on the bacillus, similar to that produced by streptomycin and isoniazid, except that it is achieved mechanically by creating a serious oxygen deficiency at the point of disease. In this respect, extrapleural collapse is even more valuable than present drug therapy, for it is as effective against strains of bacilli resistant to the various drugs as against those still sensitive. Moreover, the inhibitory action of the extrapleural collapse can be maintained indefinitely, even for years after the drugs have lost their potency. This effect of collapse is poorly appreciated and is, therefore, rarely emphasized,[1] yet this is essentially the mechanism of cure by collapse. The supporting evidence of the injurious effect of oxygen starvation on the tubercle bacillus is voluminous and fully convincing.[2] Attention, however, should be called to the recent findings reported by Dubos.[3] Dubos stated that oxygen deprivation not only disturbs the respiratory system of the bacillus directly in the manner stated but also alters unfavorably the biochemical environment within the necrotic lesion. He found that certain chemical substances, such as long-chain fatty acids and lactic acid, present in the tuberculous lesion, may become sufficiently bactericidal in low concentrations under semi-anaerobic conditions to kill the tubercle bacillus when its oxygen intake is lowered. A sort of chain reaction is thus set up, with chemical factors in the lesion acting as unexpected antituberculosis agents, "closing in" on the bacillus already weakened through oxygen starvation. Oxygen starvation of the bacillus, resulting from the walling off of the tuberculous process by the natural forces of the body so that the lesion does not communicate with a patent bronchus, and the action of the above chemical factors undoubtedly constitute part of the mechanism of spontaneous healing in tuberculosis.

Oxygen starvation of the tubercle bacillus is also the outstanding accomplishment in extrapleural pneumothorax. By preventing replenishment of atmospheric air through closure of terminal bronchioles, extrapleural collapse applies on a large scale, and in a controlled and scientific manner, the very mechanism of cure so successfully employed by nature, for it converts open, oxygen-rich lesions into closed, oxygen-poor ones and prevents closed lesions from becoming open. Since closed lesions constitute a highly unfavorable environment for the survival of the bacillus, if kept closed by the collapse they invariably heal and need no resection.

A cavity in which the walls can be approximated and the draining bronchus closed behaves in the same way as a closed lesion. The tubercle bacillus, deprived of oxygen by the collapse and weakened still further by the chemical factors in the lesion, becomes attenuated; the infection subsides, and the cavity undergoes contraction and finally obliteration. It may leave behind no visible trace or may be represented by a few scars and calcified spots. The surrounding alveoli, in the meanwhile, expand

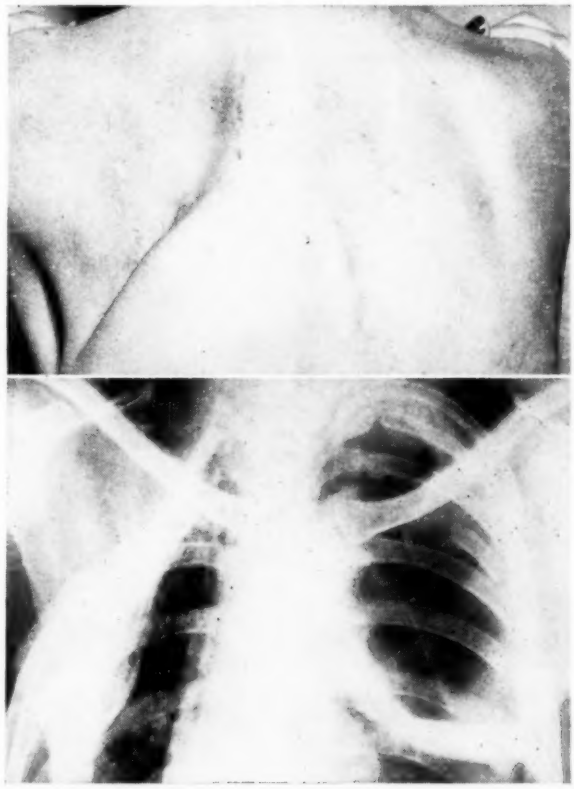

Fig. 1.—Comparison of selective thoracoplasty done on the left and extrapleural pneumothorax on the right.

to fill out the space formerly occupied by the destroyed lung tissue. A good example, but not an exceptional one, is the disappearance of the large apical cavity (4 by 3.5 cm.) in case 7 with extrapleural pneumothorax collapse. It is literally amazing how much of the diseased area,

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2. Corper, H. J.; Lurie, M. B., and Uyei, N.: The Variability of Localization of Tuberculosis in the Organs of Different Animals: Importance of Growth of Tubercle Bacilli as Determined by Gaseous Tension, Am. Rev. Tuberc. **15**: 65-87 (Jan.) 1927. Richardson, H. B.; Shorr, E., and Loebel, R. O.: Comparative Studies in the Respiratory Metabolism of Various Acid-Fast Bacilli, Nat. Tuberc. A. Tr. **27**: 205, 1931. Kempner, W.: Oxygen Tension and the Tubercle Bacillus, Am. Rev. Tuberc. **40**: 157-168 (Aug.) 1939. Rich, A. R., and Follis, R. H., Jr.: The Effect of Low Oxygen Tension upon the Development of Experimental Tuberculosis, Bull. Johns Hopkins Hosp. **71**: 345-363 (Dec.) 1942.

3. Dubos, R. J.: Discussion on Treatment of Tuberculous Meningitis and Survival of Bacilli in Tuberculous Lesions, Am. Rev. Tuberc. **65**: 637-640 (May) 1952.

previously refractory to all other therapy, can disappear under collapse and leave little or no trace behind.

In retrospect, and viewed from the standpoint of the completeness of the collapse and the resultant degree of oxygen starvation, it becomes obvious at once that virtually all poor results in patients who are given collapse therapy can be attributed to inadequate, poor, or inexpertly applied collapse. On the other hand, an area of lung well collapsed invariably heals, regardless of ultimate outcome. For instance, in ineffectual intrapleural pneumothorax there is always an area of lung that, by chance, is technically well collapsed. Such an area always improves, despite the fact that it is surrounded by progressive and fatal disease.

The whole question of what constitutes good treatment in tuberculosis has to be reevaluated in the light of these facts. If tubercle bacilli die or remain harmless in closed tuberculous lesions, as current studies on resected lungs

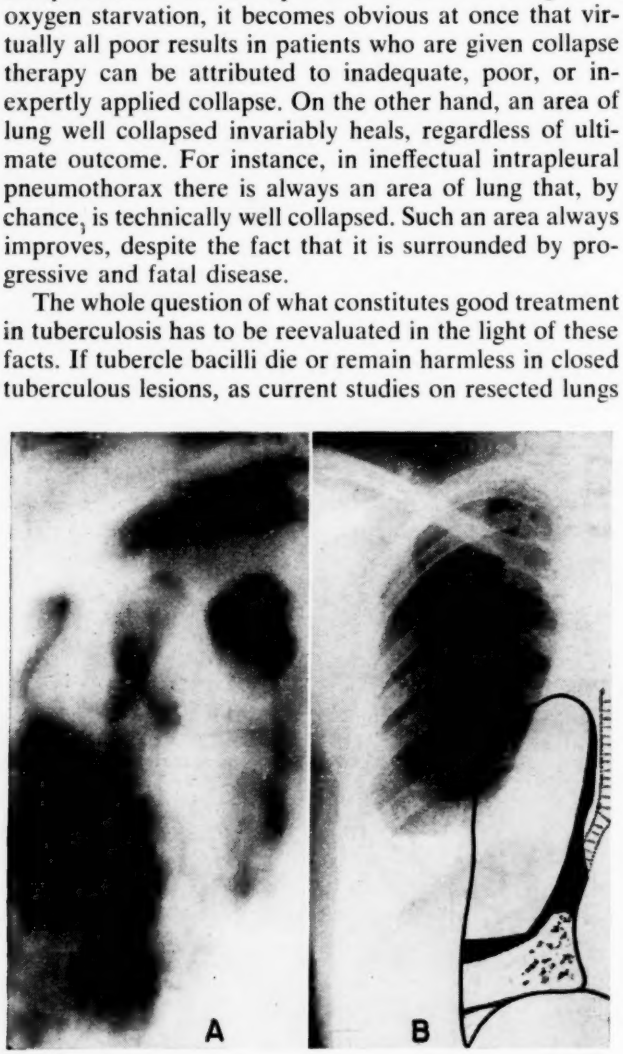

Fig. 2.—Extrapleural pneumothorax in case of acute progressive tuberculosis. *A*, planigram study of right lung after unsuccessful intrapleural pneumothorax. *B*, seven weeks after successful right extrapleural collapse.

clearly indicate,[4] and the disease heals, it would appear that major resection, with its needless sacrifice of lung tissue, increased operative risk, and prolonged hospitalization, may be ill-advised and collapse the procedure of choice. What is clearly and undoubtedly needed for many patients is a reversible collapse, similar to intrapleural pneumothorax but without its limitations and potential complications, one that will permit future use of the diseased lung after it has healed. Extrapleural collapse admirably fulfills these requirements; major resection or thoracoplasty obviously cannot.

Extrapleural collapse contributes still further to recovery: 1. Intensive rest is generally accepted as a basic principle in the treatment of pulmonary tuberculosis. Extrapleural collapse provides the most intensive rest possible and does so for an indefinite period of time. It thus promotes healing of the lung in the same sense that a cast heals a broken leg. 2. Once the diseased portion of the lung has been physically reduced to a minimum by the collapse and the blood and lymph current slowed through mechanical blockage of these channels, toxemia with all its attendant symptoms disappears promptly and the sputum becomes normal. The relatively short time required for collapse to produce a feeling of clinical well-being and normal sputum is one of the wonders of modern medicine, with far reaching social, economic, and public health implications.

Extrapleural collapse, therefore, unquestionably represents sound scientific treatment, direct and definitive. Through suppression of the infection, it can alter in dramatic fashion the reaction of the lung in tuberculosis from one of apparent extreme susceptibility to that of apparent high resistance and thus give the healing forces of the body the opportunity and the time to create the necessary immunity, which alone can bring about lasting cure. Fully integrated with bed rest, supportive measures, and chemotherapy, extrapleural collapse can create miracles of healing.

INTRODUCTION OF EXTRAPLEURAL COLLAPSE

Although extrapleural pneumothorax is potentially the most useful of surgical procedures, it is also, unfortunately, one of the most controversial. The objective is to create a selective extrapleural pocket between the outer layer of the pleura and the chest wall and maintain it by air pressure. This is accomplished by mobilizing the lung extrapleurally after resection of about 5 cm. of the fourth or fifth posterior rib through a small paravertebral incision, beginning at the transverse process. In one case (fig. 1) thoracoplasty was done on the left side in September, 1941, and extrapleural pneumothorax on the right in October, 1950. The extent of the disease at the time of surgery was about the same in both upper lobes. The thoracoplasty resulted in a deformity, but the extrapleural pneumothorax did not; the latter procedure was much more complete. The patient is now in good health, is physically active, and has normal sputum.

Extrapleural collapse, of course, is not a new operation. It was first tried by Tuffier in 1891 for pulmonary hemorrhage. During the 30's the operation was popularized by Zorini (1933) Graf (1937), and Schmidt (1937). In 1940 Dolley [5] and associates reviewed about 2,000 operations from 27 clinics and concluded that extrapleural pneumothorax should be instrumental in obtaining sputum conversion in 63% of the cases. In spite of these encouraging reports, the procedure soon fell into disrepute, particularly in this country, and it was, to a large extent, abandoned because of the numerous complications encountered and the relatively few good late results. Another reason for the current lack of popularity of this operation is the difficult and painstaking postoperative care and follow-up essential for a good result. In contrast to thoracoplasty or resection, the extrapleural collapse patient needs constant and skilled attention and protracted refills.

4. Medlar, E. M.; Bernstein, S., and Steward, D. M.: Bacteriologic Study of Resected Tuberculous Lesions, Am. Rev. Tuberc. **66**: 36-43 (July) 1952. Beck, F., and Yegian, D.: Study of Tubercle Bacillus in Resected Pulmonary Lesions, ibid. **66**: 44-51 (July) 1952. Yegian, D.: Biology of Tubercle Bacilli in Necrotic Lesions, ibid. **66**: 629-631 (Nov.) 1952.

5. Dolley, F. S.; Jones, J. C., and Skillen, J.: Extrapleural Pneumothorax: Critical Survey, Am. Rev. Tuberc. **41**: 403-422 (April) 1940.

In retrospect, this operation was introduced too soon, in the preantibiotic era, and before lytic enzymes and the necessary technical improvements were developed. During the past few years, however, chiefly since 1946, the prognosis of this operation has materially improved, due to a number of factors: the availability of penicillin, streptomycin, and other antimicrobial drugs with which to control the infection of the extrapleural space; the return to simple extrapleural pneumothorax and the discontinuance of plombage; the use of streptokinase and streptodornase to overcome fluid coagulum and blood clots with attendant loss of extrapleural space; improvements in the technique of mobilization of the lung, especially the permitting of the mesial surface of the lung to remain adherent to the mediastinum; and other innovations evolved by those who have persevered in the face of discouraging early results.[6] The serious complications that plagued extrapleural surgery in the past have, to a large extent, been eliminated or can be readily controlled. The very factors that have made resection practical have, by the same token, greatly improved the prognosis of extrapleural pneumothorax, and today old prejudices are no longer valid.

ADVANTAGES OF EXTRAPLEURAL PNEUMOTHORAX

Modern extrapleural collapse has many inherent advantages. As is evident from the accompanying illustrations and report of cases, extrapleural pneumothorax brings about the most complete and the most selective collapse possible, the ultimate in low oxygen therapy. In this respect it combines the stability of the collapse of thoracoplasty with the flexibility and versatility of the collapse of intrapleural pneumothorax; and it does so without the loss of function or deformity, or the uncertainty of cavity closure that may follow thoracoplasty, as well as without the adhesion problem, or complications or physiological disadvantages of intrapleural pneumothorax. Obviously, the more complete the collapse of the diseased area, and the better stabilized, the more intensive will be the local rest, the better the control of the toxemia, the more certain the conversion of sputum, and, above all, the greater the depressive, inhibitory effect on the tubercle bacillus. Extrapleural pneumothorax, therefore, is the most effective of collapse measures. It also offers greater security than resection, for it can bring under control virtually all the demonstrable disease in the treated lung, whereas resection is limited in its effectiveness to the area excised.

Extrapleural collapse is a one stage operation, nondeforming (fig. 1) and well tolerated, even in poor risk patients with a low respiratory reserve. It can be combined with other forms of surgical therapy on the same or contralateral side or used bilaterally. This makes it possible to extend the benefits of collapse therapy even to the patient with extensively advanced bilateral disease who otherwise could not be considered for any type of surgery. It can also be used in patients desperately ill with acute progressive tuberculosis and in the presence of serious uncontrolled pulmonary bleeding, at a time when other forms of surgical intervention may be plainly contraindicated or too risky. In all such poor risk cases extrapleural collapse may be dramatic in its effectiveness and truly a life-saving procedure. The following case histories are typical examples of the potential usefulness of extrapleural collapse in various types of cases: acute progressive tuberculosis, uncontrolled hemoptysis, advanced bilateral fibroulcerative tuberculosis, and cases of both young and old persons.

CASE 2.—A white woman, aged 33, was seriously ill with acute caseocavernous tuberculosis involving the right lung, when she came under my care on Aug. 17, 1950. The entire right upper lobe was virtually destroyed through cavity formation, and infiltrative changes were noted in the remainder of the lung. The left lung was apparently free of disease. She had a temperature of 101 F, cough and expectoration, and hoarseness, and had lost much weight. Many tubercle bacilli were found in the sputum.

Intrapleural pneumothorax was unsuccessful because of adhesions and had to be abandoned (fig. 2*A*). Thoracoplasty and resection were considered but were ruled out as too hazardous. The patient showed little improvement after therapy with streptomycin and *p*-aminosalicylic acid (isoniazid was not then available). A right extrapleural pneumothorax was performed on Sept. 29, 1950, and the disease was well controlled, with all cavities closed within one month (fig. 2*B*). The sputum became normal in March, 1951, and has remained so since. Her health is excellent today, 30 months after operation. She takes care of her home and leads a reasonably normal life.

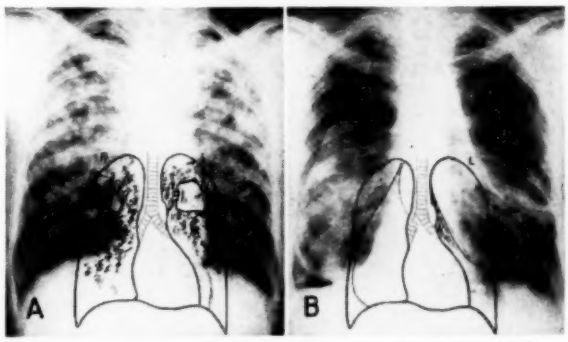

Fig. 3.—Case of far advanced bilateral disease. *A*, intrapleural pneumothorax on the left side had been unsuccessful. *B*, eight years later, the right side had collapsed with intrapleural pneumothorax (July 1, 1945, followed by pneumonolysis) and the left side with extrapleural pneumothorax (May 1, 1946). There is marked improvement in both lungs; the left extrapleural collapse is more selective and more complete than the right intrapleural collapse.

In this instance, extrapleural pneumothorax was not only dramatic in its effect but life-saving. Fortunately, since the availability of isoniazid, the chances of controlling the acuteness of the disease with drug therapy have been materially increased and the urgency for surgical intervention correspondingly lessened. Nevertheless, one can foresee cases of patients with acute disease in whom all drug therapy may fail and collapse provides the only solution.

CASE 3.—A white woman, aged 24, had advanced exudative tuberculosis with cavity formation involving the left upper lobe and bronchogenic spread to the right upper lobe, complicated by serious and continued hemoptysis. Intrapleural pneumothorax was tried on the left, but the collapse was ineffectual and had to be abandoned. The outlook appeared ominous. A left-sided extrapleural pneumothorax was established on May 9, 1947, with complete success. This patient remains well today and lives a normal life, approximately six years after surgery.

CASE 4.—A white man, aged 41, when first seen May 14, 1945, had far advanced, bilateral fibroulcerative tuberculosis with multiple cavities; the sputum showed tubercle bacilli (fig. 3*A*). Intrapleural pneumothorax on the left side (May, 1945) was unsuccessful, but that done on the right side July 1, 1945,

6. Cutler, J. W.: Importance of Extrapleural Pneumothorax in the Collapse Therapy of Pulmonary Tuberculosis, J. Thoracic Surg. **21**: 217-258 (March) 1951.

was successful, after pneumonolysis on Aug. 16, 1945. Continued bed rest and sanatorium care for one year resulted in only slight improvement of the disease in the left lung. The cavity remained open. Accordingly, a simultaneous extrapleural pneumothorax was performed on the left side on May 1, 1946 (fig. 3*B*). An excellent result has been recorded to date, seven years later; sputum is normal, the patient is working, and there is noticeable resolution of disease in both lungs.

CASE 5.—A white man, aged 61, had advanced exudative tuberculosis of the right upper lobe with a cavity 3 by 2.5 cm. in the region of the clavicle when he first came under my care on July 8, 1947. Tubercle bacilli were found in the sputum. Intrapleural pneumothorax was done, but, since the apex was found widely adherent, treatment was discontinued within a month. In the meantime, the cavity had increased in size to 6 by 6 cm. A right extrapleural pneumothorax was performed on Sept. 5, 1947. The cavity closed shortly thereafter and has remained closed, with the sputum normal since November, 1947. At present (March, 1953), the patient, aged 67, is self supporting and enjoying a normal life, nearly six years after the operation.

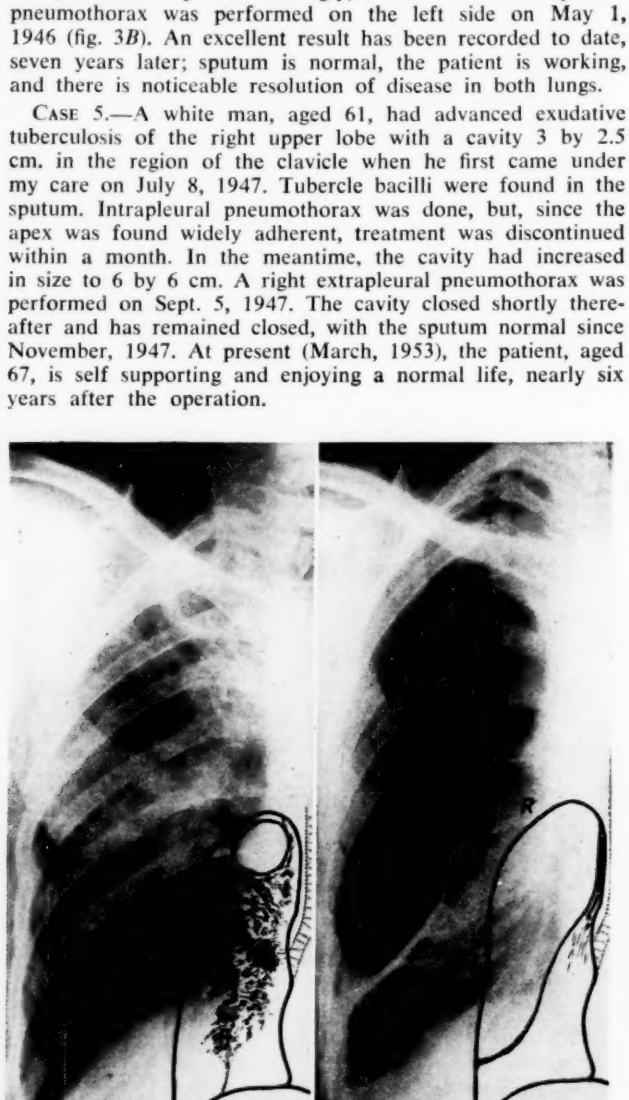

Fig. 4.—Reexpansion of extrapleurally collapsed lung, *A*, before surgery, and *B*, one month after extrapleural collapse.

Extrapleural collapse is also a happy solution for young persons who dread thoracoplasty or extensive resection and has also been carried out successfully during pregnancy.

Extrapleural collapse is a practical solution to pressing social, economic, and public health problems. Because the collapse can be established shortly after the diagnosis is made, it can bring about early effective control of the tuberculous process, early conversion of sputum and an early return to good clinical health, frequently within a matter of months. These results are possible because the collapse may be instituted in the presence of a wide variety of unfavorable clinical conditions without waiting for the disease to become stabilized and localized, as is necessary with thoracoplasty or resection, or until pleural adhesions are severed, as in intrapleural pneumothorax. Although the disease is not yet cured, the patient so restored can live a reasonably normal life, mingle freely with others, and become self-supporting. Men can go back to their accustomed jobs, women can bear children, and young persons may continue their studies. There is no reason why, in the light of the new experiences with this operation, the tuberculous patient need have his life's ambition thwarted or be forced to live a life of semi-invalidism or remain indefinitely in an institution. This is one of the truly big achievements of modern medicine—rehabilitation at its best.

Since the extrapleural collapse exerts a continuous and profound depressive effect on the bacillus years after all the drugs have lost their value, all that is needed to keep the patient in good health is to maintain the collapse long enough to permit complete healing of the tuberculous lung—empirically, for three to five years. The lengthy period of treatment is no particular hardship, or even an important inconvenience, and is a small price to pay for good health. Particularly is this true when the collapse is reversible and results in healing with little loss of lung tissue and insignificant disturbance to pulmonary function. Extrapleural collapse, therefore, not only solves the immediate pressing social, economic, and public health problems of the tuberculous patient in minimum time and at the least cost but also makes possible long-range planning and ultimate eradication of the disease. Through a more rapid turnover of patients, it can also alleviate the present shortage of hospital beds. The following report is a typical example of the potentialities in this direction.

CASE 6.—A white married man, aged 36, first came under my observation on May 5, 1949. At that time he had far advanced bilateral pulmonary tuberculosis, involving primarily the upper two-thirds of the left lung, with a cavity (2 by 3 cm.) at the apex. Closely set, flocculent spots were also present in the posterior segment of the upper section of the right lung. He had been ill with tuberculosis since March, 1943, and responded to bed rest, only to break down again in 1949. The sputum again contained tubercle bacilli. Intrapleural pneumothorax was attempted on the left side shortly after he came under my care but without success, because of an adherent pleura. On June 10, 1949, the left lung was successfully collapsed by an extrapleural pneumothorax. The cavity promptly closed, and the sputum became normal one month later (July, 1949). It has remained normal ever since and gives negative culture studies.

On Dec. 11, 1949, six months after surgery, he was discharged from the institution to continue with outpatient extrapleural pneumothorax treatment. Shortly thereafter he returned to work. At present (March, 1953) he is on the local police force and enjoys good health. He is in no way deformed or handicapped in his pulmonary reserve. The disease in the right lung, in the meantime, has improved spontaneously and needs no treatment. Here was a potentially difficult problem, solved with extrapleural pneumothorax without much hardship or prolonged hospitalization.

The importance of always preserving maximal pulmonary function in the treated lung has been increasingly recognized during recent years. Neglect of this principle can be of serious consequence to the patient should the need arise for major surgical treatment of the contralateral side, a distinct possibility in about 50% of treated patients.

Extrapleural collapse conserves pulmonary function in two ways: 1. As a surgical procedure, extrapleural collapse disturbs lung function less than either intra-

pleural pneumothorax, thoracoplasty, or resection, and very much less than resection and thoracoplasty combined in the same patient, a fact substantiated by pulmonary function studies carried out before and after surgical intervention.[7] In fact, the resultant established loss of function after extrapleural collapse is small or nonexistent and is at the expense only of functional residual air. 2. There is another aspect of the problem of pulmonary function after surgery: Good treatment must always take into consideration the indisputable fact that the tuberculous disease may clear and leave behind healthy lung. Because of the largely reversible character of the modern extrapleural collapse and the tendency for the disease to disappear under collapse, recovery can be achieved with little permanent loss of lung tissue. In contrast, lung lost through thoracoplasty or resection is gone forever.

Contrary to past experiences and commonly held beliefs, modern extrapleural collapse, relieved of empyema and of serious fluid problems, is, in my experience, largely a reversible collapse—more so than intrapleural pneumothorax. This is true even when the patient is given extrapleural collapse therapy for a period of years. The physical factors operating in the extrapleural space always favor long-term reexpansion of the collapsed lung. The following case illustrates this point, as well as many others stressed in this paper.

CASE 7.—A white man, aged 26, came under my care on April 27, 1947. Examination revealed far advanced disease involving the right lung, a cavity (4 by 3.5 cm.) at the apex, and infiltration extending as far down as the diaphragm, centering chiefly in the third and fourth anterior interspaces (fig. 4*A*). The left lung was apparently successfully collapsed with intrapleural pneumothorax, which had been maintained since October, 1944. Intrapleural pneumothorax was attempted on the right side to control the disease in this lung, but without success. Thoracoplasty or resection was considered too risky. Accordingly, an extrapleural pneumothorax was carried out on Sept. 19, 1947, and an excellent result obtained (fig. 4*B*). The cavity was closed, the disease in the remainder of the lung controlled, and the sputum rendered normal within a few weeks. The patient now had bilateral collapse: intrapleural collapse on the left side and extrapleural on the right. Within six months he returned to part-time work and left my care in August, 1949, in good health.

The intrapleural pneumothorax on the left side was discontinued elsewhere November, 1949, and the lung permitted to reexpand. The extrapleural collapse on the right side, however, was maintained. The patient continued to do well. In January, 1952, he started to cough and tubercle bacilli were again found in the sputum. He returned to my care on April 14, 1952. Planigram studies revealed at least one certain cavity in the apex of the reexpanded left lung. The heart and mediastinum were pulled over to the left, and the left diaphragm was more or less fixed and immobile. In addition, there was a fluid cap over the left apex in the area where the lung failed to reexpand. In contrast, the extrapleural collapse of the right lung was virtually the same in extent as shortly after the operation (fig. 5*A*). The pleural layers were thin, and there was no fluid problem. The right diaphragm was normal in contour and moved freely.

Since the extrapleural collapse had been maintained uninterruptedly for four and one-half years, it was decided to reexpand the right lung, at least in part, to restore vital capacity before undertaking surgery on the left side. There was no difficulty whatever in reexpanding the extrapleurally collapsed lung. There was no shifting over of the trachea or mediastinum, no distortion of the diaphragm, and no fluid problem during the reexpansion process (fig. 5*B*). In the planigram of the reexpanded right apex there were a few calcified spots but no evidence of the original large cavity (fig. 6).

On Sept. 26, 1952, an extrapleural pneumothorax was established successfully on the left side and the simultaneous extrapleural pneumothorax on the right maintained without difficulty. If this patient had been subjected to a thoracoplasty on the right side or lobectomy and concomitant thoracoplasty in October, 1947, instead of a reversible extrapleural collapse, he would have been seriously handicapped in his pulmonary reserve five years later when the disease recurred in the left lung. As it was, he left the institution on Dec. 13, 1952, free of symptoms and with sputum negative by culture. At present, (March, 1953) he is living a reasonably normal life and is self-supporting. All he has to do in the line of treatment is report for refills. He is also continuing with long-term combined drug therapy. The prospects for lasting recovery are excellent. The disappearance of the large cavity under collapse in this instance is striking but not at all exceptional.

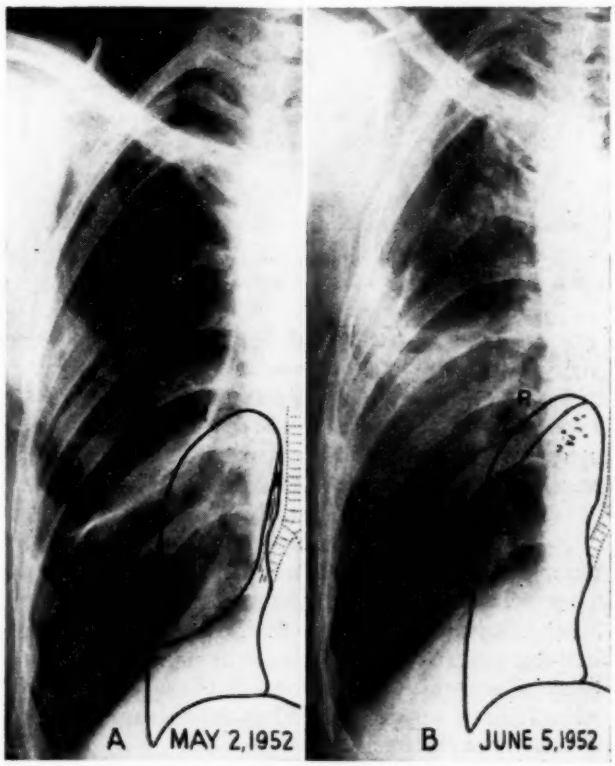

Fig. 5.—Same patient as in figure 4. *A*, four and one-half years later. *B*, one month later, after reexpansion of the right extrapleurally collapsed lung. Note thinness of the pleural layers after 57 months of continued collapse.

COMPLICATIONS, MORTALITY, AND LATE RESULTS

It is evident from what has been said and from the examples cited, that extrapleural pneumothorax is an exceedingly valuable procedure with a wide field of usefulness. My experience with 129 extrapleural operations in a consecutive series of 121 patients (8 cases of bilateral operations) from December, 1938, to May, 1950, evaluated over an average period of 54 months, has been reported on at some length in a previous communication [6] and will be brought up to date in detail in a forthcoming paper. Suffice it to say that new experiences with an addi-

7. (*a*) Gaensler, E. A., and Strieder, J. W.: Pulmonary Function Before and After Extrapleural Pneumothorax: Comparison with Other Forms of Collapse and Resection, J. Thoracic Surg. **20**: 774-797 (Nov.) 1950. (*b*) Stead, W. W.: Physiologic Studies Following Thoracic Surgery: Immediate Effects of Upper Lobectomy Combined with 5-Rib Thoracoplasty, ibid. **25**: 194-204 (Feb.) 1953.

tional 69 consecutive operations, including poor risk patients with far advanced bilateral disease and deteriorated health, continue to support the published findings.

Operative mortality and incidence of important complications will naturally vary with the type of case subjected to operation. The cumulative experience with the entire series of 198 consecutive operations as of March, 1953, is shown in figure 7. To better evaluate this experience, the results are presented as two distinct series of

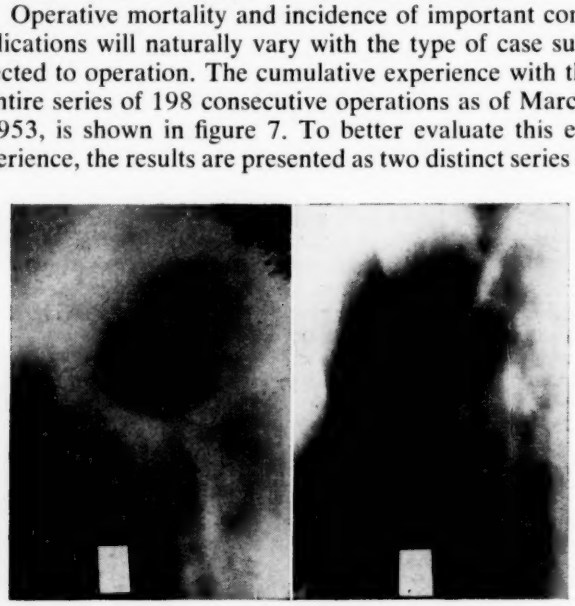

Fig. 6.—Same patient as in figures 4 and 5. Note disappearance of large cavity under extrapleural collapse in right side of figure.

operations, those performed during 1938-1946, comprising 64 consecutive operations, and those performed during 1947 through March, 1953, consisting of 134 consecutive operations. Prior to 1946 is the pre-streptomycin era and the period of experimentation, when contraindications had yet to be learned first hand and techniques improved. This is a good record, particularly when one considers the type of patients who were subjected to surgery: 59% had far advanced bilateral disease, and many were not suitable for any other form of effective therapy. Some of the unsuccessful results (seven cases) were due to inability to physically mobilize the lung, and the operation was abandoned without harm to the patient. Other failures can be avoided in future series of cases through more careful attention to detail.

Almost all serious difficulties encountered today are concentrated within the first postoperative week. Once this period is safely past and the collapse well established, extrapleural pneumothorax becomes relatively easy to manage. The fear of late infection of the extrapleural space is not borne out by recent experience. With modern antibacterial drug therapy, serious infection of the extrapleural space is uncommon and the possibility of infection decreases with long-term drug therapy. Fluid, sufficient to require aspiration, may occur from time to time but usually disappears under simple management and is not troublesome. The aim should always be to keep the space dry. The problem of what to do with the extrapleural space when treatment has to be terminated should not be magnified. It is not the serious question one is usually led to believe. In most instances, based on present observations, the lung will reexpand; in others the residual space can be allowed to fill with serum, or safely converted into a selective oleothorax.

These remarks should not be interpreted as implying that a new wave of enthusiasm for use of extrapleural surgery is in order or that other procedures should be pushed aside when plainly indicated or preferred. This would be highly undesirable and is certainly not the purpose of this paper. On the contrary, extrapleural pneumothorax, despite its many advantages, should not be undertaken lightly, for the immediate postoperative management is difficult, time-consuming, and full of pitfalls. Close attention to detail before, during, and long after the operation, and planned use of modern drug therapy are the determining factors in ultimate success. In contrast to thoracoplasty or resection, the extrapleural collapse necessitates constant attention. In fact, extrapleural collapse is a continuous long-term procedure, a one man task or a project for a closely working team. The operation, therefore, should certainly not be used in excess or when indications are lacking. On the other hand, when indications are clear, the gratifying late results fully justify all effort.

SUMMARY AND CONCLUSIONS

There have been rapid and radical changes in the treatment of pulmonary tuberculosis in recent years. Major emphasis today seems to be on drugs and resection surgery, despite the much-needed help available from collapse therapy. Careful study clearly indicates that both resection and collapse are needed, in different types of patients, and that collapse therapy remains an indispensable and important part of good treatment.

Collapse therapy has much to recommend it; the profound depressive effect on the tubercle bacillus is an exceedingly important factor, which is frequently not appreciated. Through closure of terminal bronchioles, collapse deprives the bacillus (a strict aerobe) of vitally needed oxygen, causes it to die or become attenuated, gives the body a chance to build immunity, and results in recovery. In this respect, collapse has one decided advantage over all present antituberculosis drugs: It acts as well against bacilli resistant to the drugs as against those still sensitive, and its effect lasts long after the drugs have lost their value.

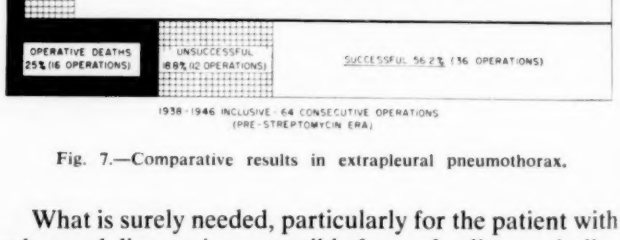
2.9% (4 OPERATIONS)
8.3% (11 OPERATIONS)
1947-1953 (MARCH) INCLUSIVE-134 CONSECUTIVE OPERATIONS
SUCCESSFUL 88.8% (119 OPERATIONS)
OPERATIVE DEATHS 2.5% (16 OPERATIONS)
UNSUCCESSFUL 16.8% (12 OPERATIONS)
SUCCESSFUL 56.2% (36 OPERATIONS)
1938-1946 INCLUSIVE-64 CONSECUTIVE OPERATIONS (PRE-STREPTOMYCIN ERA)

Fig. 7.—Comparative results in extrapleural pneumothorax.

What is surely needed, particularly for the patient with advanced disease, is a reversible form of collapse, similar to intrapleural pneumothorax but without its limitations or potential complications. Extrapleural pneumothorax, expertly performed and managed, admirably fulfills this need.

Since 1946, many important advances have been made in extrapleural collapse technique, which have freed this procedure of its former major complications and objections. Today it offers many advantages: 1. It is effective and well tolerated under a variety of unfavorable clinical

conditions at a time when other forms of surgery are unavailable or inadvisable. 2. Because it acts quickly, it offers a practical solution to social, economic, and public health problems. 3. It disturbs lung function less, and because the collapse is reversible it salvages diseased lung tissue, important considerations in cases of recurring disease.

Seven cases of a consecutive series of 186 are reported to demonstrate the usefulness of extrapleural collapse in acute progressive tuberculosis, uncontrolled hemoptysis, advanced bilateral fibroulcerative tuberculosis, and in elderly and young patients.

Despite its many advantages, extrapleural collapse should not be undertaken lightly or when indications are lacking. The postoperative management is difficult, exacting, and time consuming. Moreover, the procedure is followed by a protracted refill period. But when indications are clear, the excellent late results fully justify all effort.

2109 Spruce St.

IMPENETRABLE CICATRICIAL OBLITERATION OF THE THORACIC ESOPHAGUS

TREATMENT BY COMBINED THORACOTOMY AND ENDOSCOPY, WITH REPORT OF TWO CASES

Jorge de Castro Barbosa, M.D., R. Martinho da Rocha, M.D.
and
F. Carneiro da Cunha, M.D., Rio de Janeiro, Brazil

In the majority of cases of cicatricial esophageal stricture caused by ingestion of caustics, such as sodium hydroxide (lye), the lumen is safely penetrable endoscopically and dilatations, either peroral or retrograde, through a gastric stoma, can be carried out in an efficient manner, with good anatomic and functional results, when handled by a competent bronchoesophagologist. The combination of peroral and retrograde esophagoscopy with stereofluoroscopy can accomplish much in enabling the endoscopist to penetrate the strictured portion completely and safely; however, in about 3 to 5% of cases more radical measures are needed.[1]

Adams and Hoover [1b] apparently can be credited as the first to have employed thoracotomy in combination with endoscopic treatment of a corrosive stricture of the thoracic part of the esophagus. The obliterated portion was perforated by a metal suction catheter introduced into the distal part of the esophagus through a gastric stoma. Then a thread, which previously had been placed in the proximal portion of the esophagus, together with sodium chloride solution, was aspirated into the distal portion. Shortly thereafter, Barreto,[1a] working independently, devised more efficient instruments with which to carry out this recanalization. He, in collaboration with de Freitas,[2] in São Paulo, Brazil, performed the first operations. Later, in 1947, Botelho,[3] also in São Paulo, employed Barreto's technique in two cases.

In our series of 40 cases we employed Barreto's [1a] method in 2 and were successful in both. The technique we employed is as follows: With the patient supine, anesthesia is induced by means of intravenous injection of pentobarbital sodium and an intratracheal tube is placed to enable respiration to be mechanically controlled. Retrograde esophagoscopy is carried out via a gastric stoma constructed at a previous operation. The esophagoscope is advanced through the cardia as far into the esophagus as the obstruction permits. The instrument is anchored to the abdominal wall with adhesive tape. Next, peroral esophagoscopy is carried out, using a scope of wider diameter than the first. This instrument is carried as far down as possible into the esophagus and is anchored to the patient's mouth with tape.

The patient is then moved to a left lateral position, in preparation for right thoracotomy. Access is through an intercostal space or the bed of a resected rib. Usually the fifth, sixth, or seventh rib is removed to gain access to the midthoracic segment of the esophagus. The patient is then anesthetized with nitrous oxide and oxygen supplemented by curare. The patient's abdomen is placed as near the edge of the operating table as possible, and the sterile drapes are so placed as to leave an ample screened-off space in which the esophagoscopist who handles the retrograde scope can work with ease. The main maneuvers will be carried out through this scope. It is helpful to this endoscopist to see, also extraesophageally, the progress of his maneuvers. For this purpose a fairly large mirror may be placed above the thoracic operative field in such a way as to permit all movements of the retrograde scope to be reflected and seen by the esophagoscopist from his position at the proximal end of the abdominally-placed scope.

The lung is retracted anteriorly, and the mediastinal pleura is cut longitudinally to expose the desired segment of esophagus. There is no need to crush the phrenic nerve, since the diaphragm need not be immobilized. Depending on the upper level to which the esophagus has to be mobilized, it may be necessary to section, between ligatures, the arch of the azygos vein as it joins the superior vena cava. This was necessary in one of our cases, since the lower end of the upper scope could be felt and the glow from the illuminating bulb could be seen through the esophagus under this vein. The edges of the pleura are dissected anteriorly and posteriorly and retracted by

1. (*a*) Barreto, P. M.: Atresias do esôfago, read before the First Pan American Congress of Otolaryngology, Chicago, 1946; reviewed, Rev. paulista med. **32**: 250 (April) 1948. (*b*) Adams, R., and Hoover, W. B.: Corrosive Stricture of the Esophagus, with Function Restored by Combining Surgical and Endoscopic Treatment: Report of a Case, Lahey Clin. Bull. **3**: 250 (April) 1944.

2. de Freitas, J. M., cited by Barreto.[1a]

3. Botelho, J. A. de A., in discussion on Barreto.[1a]

means of long, thin threads of silk tagged with forceps. These threads may be used later to suture the mediastinal pleura.

The esophagus is then carefully dissected out of its bed and is mobilized enough to straighten its normal curvature and permit the esophagoscopes to be placed

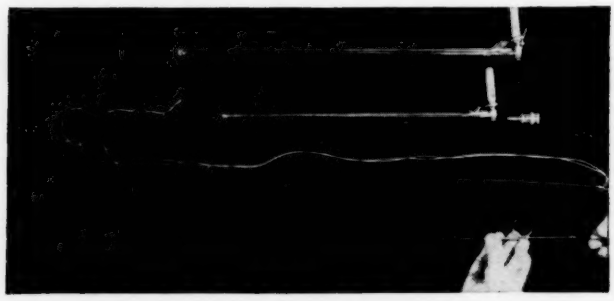

Fig. 1.—Instruments used for recanalization of the esophagus with cicatricial atresia; from below upward: (1) cannula in left hand and proximal end of screwed-in stopper in right hand, (2) long needle with triple-cutting edges at tip, threaded with double strand of no. 2 cotton thread, (3) smaller esophagoscope used in a retrograde direction through gastric stoma, and (4) larger scope with wider lumen used perorally.

more nearly in the same axis. One will find at this point that it is possible to advance the scopes even further. Thus, their extremities can be more nearly approximated than was feasible previously. The dissection of the periesophageal tissue should be carried out away from the esophagus so as not to damage its muscle. Care should be taken also to preserve the vagus nerves. This dissection is the most delicate phase of the operation, and haste should not be allowed to defeat the purpose of the surgeon to preserve as much as possible of the wall of the esophagus. As the dissection progresses at the site of the involved segment, the number of muscular fibers that can be spared is unexpectedly large. Finally, a fairly muscular walled segment of esophagus is seen, although at first the esophagus appeared to be considerably destroyed.

At this point the esophagoscopist who handles the retrograde scope may begin his maneuvers in collaboration with the surgeon. The instruments are represented in figure 1. A long, thin cannula, supplied with a stopper that is screwed in at the proximal end, is advanced through the lumen of the retrograde scope. It is found that the cannula can be advanced further than the scope into a narrowed portion of lumen that tapers off into the obstructed portion. Then the surgeon, using cotton gloves over his rubber ones to prevent slipping, "dresses" the esophagus over the end of the cannula, making it advance now even further. The ends of the scopes are now found to be apart only half the distance that was seen between them in the roentgenogram taken preoperatively. (Compare figure 2*B* with figure 2*C*).

The stopper now is removed from the cannula, and a long needle (fig. 1), with three cutting edges at the tip, is introduced through the cannula and made to perforate completely the atresic esophageal segment. This is done under the direct guidance of the surgeon, who conducts the needle safely into the wider lumen of the upper scope. Any inadvertent perforation can be sealed immediately by the surgeon. The esophagoscopist whose instrument is above the stricture sees the tip of the needle as it emerges in his field. Already it is threaded with a double strand of no. 2 cotton thread. The needle is pulled out through the upper scope, and the cotton threads are left in place. The upper ends of the threads are brought out through a nostril and are tied to the lower ends, which make their exit through the gastric stoma. Figure 2*B* is a roentgenogram taken in the course of the operation, with the two scopes, the cannula, and the needle passing into the lumen of the upper scope.

The dissected segment of esophagus is then encircled by strands of oxidized cellulose gauze, which are left in place. The mediastinal pleura is sutured. The lung is allowed to reinflate, and the thoracic wall is closed except that a catheter is left in the pleural cavity for drainage through the 10th interspace. Continuous underwater sealed suction is employed. The catheter may be removed after 24 or 48 hours and the patient allowed to get up.

The threads are replaced every five days to prevent deterioration. Retrograde dilatations effected via the gastric stoma may be begun 5 to 10 days postoperatively. A "train" of three consecutive rubber Tucker bougies is used at each session. This is continued periodically until metal dilators can be introduced perorally, just as they are employed in treatment of any partial or incomplete esophageal stricture. The patients should be followed closely for the first months and periodically thereafter. During the process of epithelization, small exuberant areas of granulation tissue should be carefully cauterized endoscopically.

REPORT OF CASES

Case 1.—A woman, 23 years old, related that accidentally she had ingested sodium hydroxide 20 years previously. Some form of bougienage had been attempted. When the patient

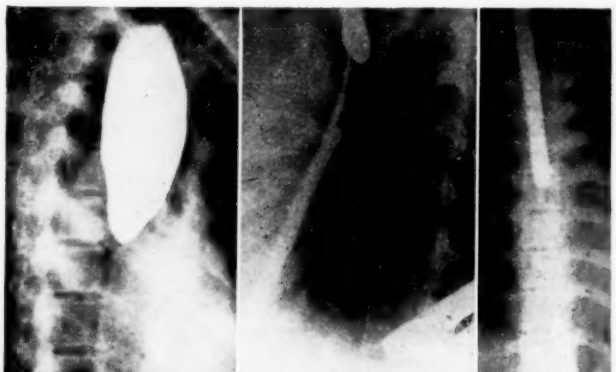

Fig. 2.—Roentgenograms taken in case 1. *A*, preoperative roentgenogram demonstrating complete obliteration of the thoracic portion of the esophagus at a level about 5 cm. below the arch of the aorta. *B*, roentgenogram taken in the course of the operation, showing the ends of the two scopes, the tip of the cannula coming out of the lower scope, and the needle already introduced through the cannula and into the lumen of the upper scope. *C*, anteroposterior roentgenogram showing obliterations of the esophagus from the level of the 7th to level of the 10th thoracic vertebrae. This distance was considerably decreased at operation.

was 3 years of age gastrostomy had been performed for feeding. The gastric stoma had been kept open by permanent use of a thick rubber tube. Through this all nourishment and water was instilled. The patient had to regurgitate swallowed saliva

every hour or so. Two hours was the most that could elapse without regurgitation. From lack of chewing the patient had lost all her teeth, and upper and lower plates had been placed. The woman was undernourished and underweight. Physical examination otherwise gave essentially normal results, and results of routine laboratory examinations were reported to be within normal limits. Roentgenograms of the esophagus after she had swallowed a suspension of barium appeared

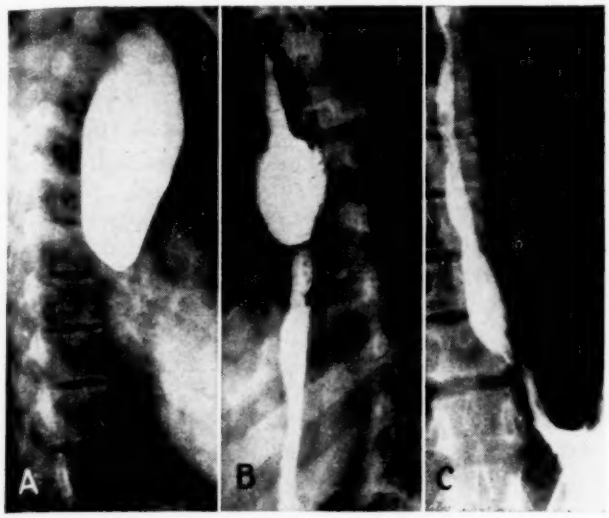

Fig. 3.—Roentgenograms taken in case 2. *A*, preoperative roentgenogram, showing lower end of proximal part of esophagus at a level 5 cm. below the aortic arch. Other examinations failed to demonstrate a lumen immediately below the level of the obstruction. *B*, roentgenogram taken three weeks postoperatively and after two weeks of treatment; the patient had undergone four dilatations and could eat any pasty food and liquids, liberally. *C*, recent roentgenogram showing normal roentgenologic appearance of the esophagus.

as in figure 2*A*. Similar roentgenograms were made using more fluid contrast mediums. Simultaneous peroral and retrograde esophagoscopy (fig. 2*C*) was carried out. Multiple attempts to penetrate the obstructed esophageal segment failed.

After the patient had reached a good nutritional state, recanalization of the esophagus by means of bidirectional esophagoscopy and thoracotomy combined was carried out with the technique previously described. The thorax was entered through the bed of the resected sixth rib on the right side. The arch of the azygos vein, as it entered the superior vena cava, had to be sectioned between ligatures.

The postoperative course was uneventful. The pleural drainage tube was removed 24 hours postoperatively, and the patient was out of bed 24 hours later. Retrograde dilatations with rubber Tucker bougies were begun five days postoperatively. Use of these was followed by employment of oral metal dilators. The patient was eating everything she wished about three months postoperatively. Six months after the operation roentgenograms disclosed that the upper third of the esophagus was moderately dilated and that the lumen was slightly narrowed at the old site of stenosis. Fourteen months have elapsed now since the operation. Recently, on esophagoscopic examination, the recanalized segment was seen to be completely epithelized.

Case 2.—A woman, 19 years of age, related that she had ingested sodium hydroxide for suicidal purposes almost three years prior to her admission. Bougienage had not been attempted. A gastric stoma had been constructed, through which all food was instilled. The preoperative roentgenogram of the esophagus is represented in figure 3*A*. Similar roentgenograms were made after the patient had swallowed more fluid contrast mediums. Simultaneous peroral and retrograde esophagoscopy, with insufflation of air, was carried out. Multiple attempts at penetrating the obstructed esophageal segment failed. The patient was undernourished and underweight. Physical examination otherwise gave essentially normal results, as did routine laboratory examinations.

After adequate preoperative preparation, including use of a high caloric, high protein diet and vitamin supplements, the operation described earlier was carried out. The right side of the thorax was entered through the bed of the resected sixth rib. The arch of the azygos vein was left intact. The pleural drainage tube was removed 48 hours postoperatively, and the patient was allowed to get up. The postoperative course was smooth.

Figure 3*B* is a roentgenogram of the same patient three weeks postoperatively and after two weeks of treatment. Dilatation had been done four times. The proximal portion of the esophagus is still somewhat dilated, and a short part of the lumen is still narrowed. Figure 3*C* shows that the roentgenologic appearance of the esophagus is normal. Esophagoscopic examinations by two of us (R. M. R. and F. C. C.) revealed that the esophagus was normally epithelized.

This woman was operated on more than a year ago. The gastric stoma closed spontaneously, and the functional result was excellent.

SUMMARY

In two cases of esophageal stricture caused by ingestion of sodium hydroxide (lye) thoracotomy and endoscopy, according to the technique of Barreto, were successfully applied. Esophagoscopes were introduced nearly simultaneously, one through the mouth and the other through a previously made gastric stoma. Thoracotomy was performed and the esophagus exposed. In one case the arch of the azygos vein had to be cut between ligatures. The exterior of the esophagus as it lay in the surgeon's field was made visible by means of a mirror to the endoscopist who handles the retrograde instrument. The upper and lower portions of the esophagus were brought into the same axis, and the distal ends of the two esophagoscopes were approximated as closely as possible. A long cannula was introduced through the retrograde scope and advanced into the narrowed portion of the esophagus below the stricture. The surgeon "dressed" the esophagus over the cannula as far as possible. A long needle, bearing threads, was introduced through the cannula and was thrust through the atresic portion of the esophagus into the upper esophagoscope. The threads, brought out through a nostril and the gastric stoma, were used to carry dilators. The patients were promptly out of bed. Results were excellent.

Rua Debret 23—s. 513 (Dr. Barbosa).

The General Practitioner.—General practice, no less than the specialties, needs a leavening of exceptionally able men and women. . . . Prompt and accurate diagnosis is the foundation of successful general practice. The function of the family doctor is to understand the health problems of his patients and to recognize early the nature of their troubles. This is a large order, for his patients are unselected. They come to him with complaints that may be trivial or serious, obvious or obscure, real or imagined, simple or complicated. He must sort them out. In doing so he recognizes those needing immediate treatment from those requiring more observation and study. He decides whether he can treat the patient himself, or if help is necessary. Frequently this latter decision bears little relationship to the seriousness of the condition. He may be able to care for the most serious as well as anyone else. The first diagnosis is often the most important. Making this correctly . . . is not . . . easy, . . . but it steadily is being made easier through the many aids and facilities being placed at the disposal of the family doctor.—W. V. Johnston, M.D., The Changing General Practitioner, *University of Western Ontario Medical Journal*, March, 1953.

CURRENT THERAPY OF GOUT

Charley J. Smyth, M.D., Denver

Although there is no known cure for gout, the control of the frequency and severity of acute attacks is satisfactory with the measures available. Failure to recognize and manage acute gout leads to much unnecessary suffering and ultimate deformity. Since recent studies point to the hereditary etiology of gout,[1] relatives of patients with active gout who have hyperuricemia should live moderately and avoid obesity, fatigue, exposure to extremes of temperature, excessive trauma to joints, excessive intake of foods high in purines, and all known provocatives of acute gouty arthritis.

A consideration of the treatment of gout must, by the very nature of the disease, be divided into two parts. The now well-known diagram of Dr. Philip Hench (fig. 1) illustrates the typical pattern of the disease and indicates the pretophaceous or first stage, characterized by acute recurrent arthritis with complete remissions, and the tophaceous stage, characterized by chronic arthritis with

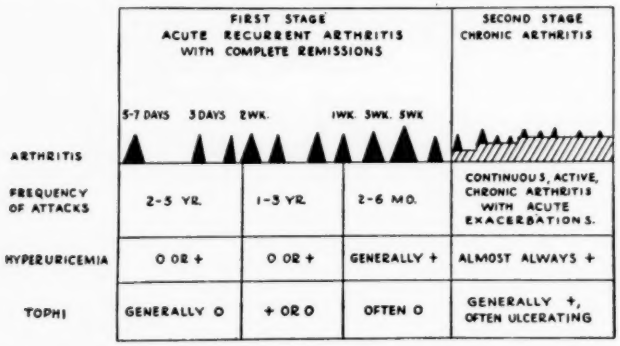

Fig. 1.—The basic pattern of the course of gout and gouty arthritis (P. S. Hench, 1936).

acute exacerbation. During the first stage, the problem of therapy is the management of the acute attacks and measures employed in the intervals to prevent future attacks. In the second stage, the aim of therapy is to relieve the pain of chronic gouty arthritis and to ward off or delay development of the complications of the disease, among which are nephrolithiasis, cardiovascular lesions, and tophi.

TREATMENT OF ACUTE ATTACK

In contrast to most of the other forms of arthritis, the treatment of gout is relatively effective, especially treatment of the acute attacks, results of which are frequently dramatic. In this discussion of current therapy, the traditional measures will be reviewed briefly and the new developments will be emphasized.

Rest.—Absolute bed rest, with elevation of the affected part and no weight bearing until the acute pain and tenderness have disappeared, is recommended. The affected part should be temporarily immobilized by means of a light splint and protected from bedclothes by the use of a cradle.

Drugs.—Colchicine: At the first appearance of symptoms of a gouty attack, colchicine, the alkaloid of colchicum, should be taken. Colchicine alone is still the treatment of choice for acute attacks of gout. The recommended dose is 0.5 mg. (1/200 grain) in tablet form every hour or two hours until pain is relieved or until diarrhea, nausea, or vomiting occurs. About 10 tablets of colchicine are required in the average attack of gout although the dose may vary from 8 to 16 tablets. Many patients learn by experience the optimum number of tablets to take with each attack, so that alleviation of joint pain may be attained without undesirable gastrointestinal symptoms. The secret of effective therapy is to begin use of colchicine at the very first warning and to use enough to produce some nausea or a loose bowel movement. Use of camphorated opium tincture (paregoric) may be necessary to control the toxic symptoms. The patient should always carry a supply of this drug and start taking the pills at the first appearance of symptoms of a gouty attack. Delay of treatment for a few hours after the onset of acute symptoms may increase the severity and prolong the duration of the acute episode. Response to the drug is often dramatic. Joint pains and swelling begin to subside about 12 hours after the institution of therapy, and, in most instances, pain is completely relieved in from one to two days. Over 95% of acute attacks are materially benefited by a single course of colchicine. Should no benefit occur, a second course of colchicine should be given after an interval of three days; repetition of a course sooner may precipitate gastrointestinal symptoms. The mechanism of action of colchicine is unknown. It does not act through the mechanism of corticotropin (ACTH).[2] Recent studies using isotopically labeled uric acid suggest that colchicine might decrease the rate of uric acid synthesis.[3]

Corticotropin and Cortisone: The close relation between gouty arthritis and adrenal cortical function was demonstrated by independent investigators soon after corticotropin [4] and cortisone [5] were introduced. Gouty persons excrete subnormal amounts of 17-ketosteroids, usually about one-third of the minimal normal value for adult men.[6] A second endocrine disturbance characterized by disturbed regulation of the rate of excretion of 11-oxysteroids has recently been demonstrated in patients with clinical gout.[2b] Further evidence to establish acute gouty arthritis as a true endocrine deficiency state are the pronounced biochemical changes and clinical effects of the administration of corticotropin and cortisone in the gouty person. These hormones are capable both of provoking attacks of acute gouty arthritis in patients with quiescent gout and of causing prompt amelioration of acute gouty arthritis. Typical acute attacks of gout may be precipitated in a large proportion of interval gout patients by the administration and then withdrawal of corticotropin. In most patients the joint symptoms begin within 96 hours. This observation has lead to the conclu-

From the Department of Internal Medicine, University of Colorado School of Medicine.

Read at the Sixth Clinical Session of the American Medical Association, Denver, Dec. 4, 1952.

Because of space limitations, the bibliographic references have been omitted from THE JOURNAL and will appear in the author's reprints.

sion that, following the withdrawal of corticotropin there is an 11-oxysteroid lack, which in the normal adult is terminated by a short period of "rebound" 11-oxysteroid excess; in the gouty person this "rebound" appears deficient, and gouty attack occurs during this period of induced relative 11-oxysteroid deficiency.

When corticotropin is given to a patient during an acute attack, the symptoms promptly disappear. This rapid control may sometimes result from a single injection of 50 mg. When the hormone is withdrawn, a state of 11-oxysteroid lack is once again induced, and many patients experience a recurrence of their attack within a few days. This tendency of acute gout attacks relieved by corticotropin therapy to return after hormone withdrawal limits the use of this hormone as the sole therapeutic agent for acute gout. Fortunately, colchicine given during or immediately after treatment effectively overcomes this tendency and permits full advantage to be taken of the rapid termination of an acute attack that corticotropin can produce.[7] In the majority of acute attacks treated by concurrent administration of corticotropin and colchicine, a single 50 mg. dose of corticotropin effectively terminates the attack within four hours; in a few patients a second or a third dose at six hour intervals is required. Colchicine administration is begun at the time corticotropin is given. The dose of colchicine is 0.65 mg. (1/100 grain) four times daily until the first gastrointestinal symptoms of intolerance occur; then for 24 hours no colchicine is given. Administration of colchicine is resumed in a dose of 0.65 mg. three times daily for at least two weeks. Except in a few patients, combined corticotropin and colchicine therapy has proved effective in preventing recurrences. This new regimen is rational and appears to be the most rapid and effective method available for treatment of acute gouty arthritis.

Phenylbutazone: Phenylbutazone (Butazolidin) has a pronounced beneficial effect in the treatment of acute gouty arthritis.[8] It is a new synthetic pyrazol derivative, entirely unrelated to the steroid hormones, having the clinical designation 3,5-dioxo-1,2-diphenyl-4-n-butylpyrazolidine. Phenylbutazone was developed as a solvent of the relatively insoluble aminopyrine, and its first clinical use in various rheumatic diseases was in combination with aminopyrine in a preparation known as Irgapyrin in Europe and Butapyrin in the United States. Since July, 1951, phenylbutazone has been investigated extensively [9] and found to be as effective as the previously used mixture with aminopyrine. It is available for oral use in tablets containing 100 or 200 mg. or for intramuscular administration in a 20% solution. The average effective oral dose is 600 to 800 mg. daily in divided amounts; the usual intramuscular dose is 5 ml.

The clinical response is excellent in most acute episodes of gout that have been reported. Among the various rheumatic disorders treated, the results in acute gout are perhaps the most spectacular. With oral administration of this preparation, objective improvement of the affected joints is generally apparent within 24 hours, and, with its parenteral use, there is usually pronounced subjective and objective relief within a few hours. The pathologically elevated plasma urate level generally falls to normal or almost normal within a few days of the start of therapy. This decrease is accompanied by a corresponding increase in urinary excretion of urates. The results in one patient illustrating these changes are shown in figure 2. Note that in this patient phenylbutazone caused a reduction in the serum uric acid level and a sharp rise in the urinary uric acid level, with a corresponding elevation in the renal clearance of uric acid. The uric acid clearance returned toward normal when sodium bicarbonate was added to phenylbutazone. These observations are contrary to those of Kuzell [8b] and Kidd and co-workers.[8c] In the experience of one observer, gouty patients preferred phenylbutazone to colchicine.[8b] Undesirable reactions to phenylbutazone include morbilliform rash, edema, nausea, abdominal discomfort, anemia, vertigo, stomatitis, nervousness, thrombocytopenia, and agranulocytosis. In view of the short-term therapy required to control acute episodes of gout, it is unlikely that serious toxic manifestations will occur; however, the patient should be carefully watched for signs of toxicity.

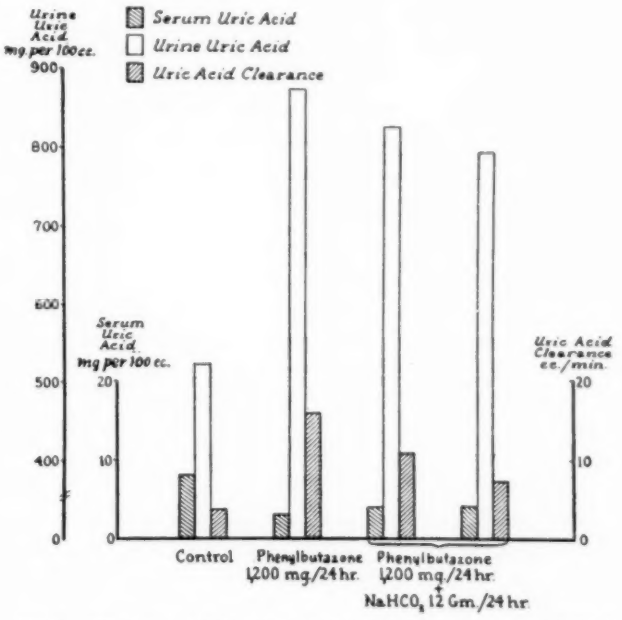

Fig. 2.—Effect of administration of phenylbutazone (1,200 mg. daily in four divided doses) on serum uric acid and urine uric acid levels and renal uric acid clearance in a 35-year-old patient who has recurrent attacks of gout.

Hydrocortisone: Beneficial effects from the parenteral and intra-articular injection of hydrocortisone (compound F) have been observed by Hollander.[10] It is not surprising that this adrenocortical steroid is capable of correcting the 11-oxysteroid lack, which is a basic metabolic defect in gouty patients with acute joint symptoms.

Diet.—Diet during the acute attack should consist of milk, eggs, cereal, fruits, and vegetables with a low purine content. A large fluid intake is indicated, and all alcoholic beverages should be avoided.

INTERVAL TREATMENT

The management of the patient with gout is not completed when the acute attack is over. This is a chronic disease for which treatment must be continued indefinitely. The aim of treatment in the interval between attacks of acute gout is to avoid or postpone the number and severity of subsequent episodes. It is in the treatment of the gouty subject between acute attacks that encourag-

ing progress is being made, but, unfortunately for both the patient and the physician, such interval management is not ideal, and the clinical cure for chronic gout is still not a reality.

In outlining a regimen for gouty patients during the intercritical and chronic gouty arthritis states attention is given to the following factors: (1) restriction of activity and avoidance of excessive trauma; (2) abstinence from use of alcohol; (3) the use of one or more of the following drugs: colchicine, probenecid (Benemid), phenylbutazone, cortisone, and cinchophen; (4) a diet low in purines and high in fats and carbohydrates; and (5) the care of tophi. Each of these measures deserves further detailed consideration.

Activity.—The pathogenesis of acute episodes that characterize this disease cannot be traced with certainty, but clinical observations for many centuries have established certain events as factors in precipitating an acute flare-up of quiescent gout. One of these factors is acute trauma to a joint. Unusual physical activity, such as excessive walking, will also precipitate a bout. A patient may be suddenly incapacitated by acute gout during his usual occupation and may attempt to place the blame on minor injury. To avoid unjust claims for an industrially connected or aggravated event, it is important to point out that dietary indiscretions, alcoholic overindulgences, minor surgical operations, the use of certain drugs (liver abstract, mercurial diuretics, or sulfathiazole), and exposure to cold and dampness are also provocative factors.

Alcohol.—Despite abstinence from the use of alcoholic beverages many patients continue to have repeated bouts of joint pain. Although evidence of the therapeutic value of such abstinence is inconclusive, it is preferable that use of alcohol be avoided, except in small amounts, and these should be permitted only if the patient insists on this privilege.

Drugs.—Colchicine: There is a conviction among some physicians that colchicine has a preeminent place in the prophylaxis of acute gout in cases in which there are recurrences of acute severe attacks. In such cases the patient regularly takes 0.5 to 1 mg. every night. In 23 cases reported by Gutman [11] this daily ingestion of colchicine together with dietary restriction of proteins and purines has proved to be by far the most effective method of minimizing the frequency and intensity of acute gouty attacks. In some instances it has made the difference between virtual incapacitation and relatively normal activity. These patients are also taught to take larger abortive doses of colchicine on the first intimation of an attack, such as pain, stiffness, or other indisposition.

Probenecid: Probenecid is a relatively nontoxic urate diuretic, which is effective in the treatment of the interval and chronic gouty arthritis stages of this disease. It was first introduced into clinical medicine as an adjunct to penicillin and *p*-aminosalicylic acid therapy. In patients with chronic gout it effectively lowers the serum urate level by blocking tubular reabsorption of glomerular filtered urates. The clinical application of probenecid was evaluated by Talbott [12] in more than 30 patients with chronic gout. With its use, blood uric acid levels promptly fell to normal and remained there even after prolonged therapy. The urinary uric acid excretion was increased 20 to 30%. Gutman [11] and Yü [13] reported the results of the use of this uricosuric agent in 14 patients and concluded that probenecid was the most satisfactory urate diuretic for protracted administration; no new tophi developed in any of their patients with chronic tophaceous gout, and in several of their patients who had received protracted therapy there was disappearance or decrease in size of tophi together with reduction in swelling of chronically enlarged joints. Administration of 0.5 gm. daily for one week followed by 1 gm. daily in divided doses is recommended. This latter dose can be given for an indefinite period. Acute attacks of gout may develop soon after the onset of therapy, but their incidence diminishes with continued therapy. If an acute attack of gout occurs during therapy, probenecid should be continued and full doses of colchicine should be administered. When aspirin is given simultaneously with probenecid, the action of the latter drug in lowering the serum urate level is completely annulled.[14] Therefore, salicylates should not be given in conjunction with probenecid, either for an analgesic or a diuretic effect. Thus far, there have been no indications of aggravated renal damage owing to the increased excretory urate load on the kidneys produced by this agent. To summarize, probenecid is of value in the long-term control of chronic gouty arthritis; it is of no value in acute attacks of gout. Although experience is limited, it appears that mobilization of gouty tophi by the protracted use of this uricosuric agent may be accomplished.

Phenylbutazone: Reports of the clinical evaluation of phenylbutazone in the second stage of gout (chronic gouty arthritis and superimposed attacks of acute gout) are few. Kuzell [8b] has treated 58 patients with chronic gout with phenylbutazone and compared the results with those in 41 other patients with chronic gout who received Butapyrin. In this comparative study there was no significant difference in the therapeutic response to Butapyrin and phenylbutazone. In 36 patients with chronic gouty arthritis maintenance therapy was employed. Twenty-seven of the 36 had decreased frequency of acute attacks as well as amelioration of the chronic gouty arthritis. Acute exacerbations in patients with chronic gout responded to increased amounts of the drug. The maintenance dose varied from 200 to 800 mg. daily. In this study most gout patients preferred phenylbutazone to colchicine. Steinbrocker and his associates [8d] administered phenylbutazone to 52 patients with painful muscular disorders; among these was one patient with chronic gout who was treated for three and one-half months, with great improvement. This patient considered his condition better during that time than when he had used cortisone. These early results are promising. Additional clinical trials are indicated to determine the incidence and severity of toxic effects. The influence of phenylbutazone on uric acid metabolism warrants extensive investigation.

Cinchophen: The use of cinchophen in chronic gout is a controversial subject. Because of its toxicity and because the same results can be obtained without the risk of complications by the use of salicylates and probenecid, cinchophen should not be used in this disease.

Dietary Restrictions.—It is widely accepted that the diet of the patient with chronic gout should be low in

purine-rich foods to relieve the already overburdened mechanism for the disposition of purines. There is no altogether convincing evidence to prove that adherence to a rigorous purine-free diet reduces the frequency of acute attacks or prevents chronic arthritis or the complications of gout. It is well established, however, that less uric acid is excreted in the urine when a regimen of reduced purine intake is followed. It appears unreasonable, therefore, to introduce unnecessary amounts of purines. A reasonably low purine intake can be obtained by eliminating sweetbreads, anchovies, sardines, liver, kidneys, and meat extracts, a restriction that offers no hardship to most patients. Further confusion with respect to the value of dietary restrictions has resulted from the recent demonstration by several groups of investigators [15] using isotopically labeled carbon and glycine that synthesis of uric acid occurs regularly from the simplest nitrogen and carbon compounds. It is clear from this discovery that all proteins, fats, and carbohydrates must be regarded as potential precursors of uric acid and that complete control of uric acid formation by dietary regulation is impossible. Although the usefulness of dietary restriction is still not established, it seems advisable in patients with chronic gout to limit the purine as well as the protein intake.

Treatment of Tophi.—If tophi of the hands or feet become large or ulcerate, excision with thorough débridement results in prompt healing and obviates the danger of infection and possible amputation. If the report of Yü and Gutman [13] can be confirmed, the prolonged administration of probenecid would be useful in reducing the size of old, established tophi and removing the urates that are deposited in involved joints and bursae.

SUMMARY

In recent years, real progress has been made in the development of new methods for the management of gout. A more rational approach to therapy, based on knowledge of the basic mechanisms of the metabolic defect in gout obtained from new methods of investigation, especially the employment of isotopes, has developed. The establishment of gout as an endocrine disease occurring in persons with hereditary susceptibility permits the physician to promptly recognize and treat the early stages of gout. Within the past few years, several new drugs have been introduced that produce profound biochemical changes and definitely influence the clinical course of this disease. The hormones corticotropin (ACTH), cortisone, and hydrocortisone (compound F) have a dramatic effect on the acute episodes of gout and provide new tools for further investigation of the pathogenesis of this illness. The concomitant use of corticotropin and colchicine, as recommended by Wolfson, offers a promising new approach to the control of acute episodes of gouty arthritis. The prolonged administration of the urate diuretic drug probenecid (Benemid) effectively removes the urates that are deposited in the joints and bursae, and recent studies in a limited number of cases have shown that its long-term use reduces the size of established tophi. The spectacular results already reported indicate that phenylbutazone (Butazolidin) may be a useful drug in both the acute and chronic stages of this disease. If the occasional undesirable effects prove not to be serious hazards, this new pyrazole derivative will be a welcome addition to the growing list of drugs of value in this crippling disease.

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TRYPSIN INHALATIONS IN RESPIRATORY CONDITIONS WITH THICK SPUTUM

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For many years one of us (L. U.) has been interested in securing an ideal preparation to dissolve the thick tenacious material that impedes the respiration of patients with bronchial asthma and other respiratory conditions. In 1937, in collaboration with Albert H. Andrews, assistant clinical professor of bronchoesophagology at the University of Illinois Medical School, an aerosol was made of an enzyme derived from the fruit of the plant Carica papaya and was tested in animals and on 10 patients. The investigation, which was unpublished, was discontinued because of severe local reactions including bleeding and marked hoarseness. Recently, our interests were drawn to trypsin, a natural body enzyme that digests necrotic tissue without producing adverse action on living tissue. The effects of this enzyme on 73 patients are herewith reported.

PHARMACOLOGY

The highly purified crystalline trypsin used in this study and available as Tryptar is derived from mammalian pancreas and is found normally in the intestinal tract. This enzyme has a broad spectrum of vigorous proteolytic action on protein, denatured protein, true peptones, respiratory and intestinal mucin, fibrin, and protein split products. The final degradation products of tryptic digestion are small polypeptides and some amino acids. Crystalline trypsin does not digest living tissue, since both serum and viable cells contain specific trypsin inhibitors as well as nonspecific inhibitory substances, which act as protective mechanisms against proteolytic digestion. This selectivity of digestion plus the absence

Tryptar was supplied by the Armour Laboratories, Chicago.

Because of space limitations, some of the tables have been omitted from THE JOURNAL and will appear in the authors' reprints.

Associate Professor (Dr. L. Unger) and Clinical Assistant (Dr. A. H. Unger), Northwestern University Medical School, and Attending Physician, Wesley Memorial Hospital (Dr. L. Unger).

Drs. Mary Karp, Jerome Head, Theodore Hudson, Edward E. Avery, Paul Rhoads, Jesse Waller, and Earl Zaus, Wesley Memorial Hospital, aided in the clinical studies. Dr. Catherine H. Roth, Assistant Medical Director, the Armour Laboratories, assisted in the program of this study. La Verne LaMarche and Tybee Sue Meyers, technologists, gave many of the inhalations. Mr. Robert R. Lee, technician in anesthesia, Wesley Memorial Hospital, gave assistance.

of antigenicity or sensitivity appealed to us, as well as to a number of other workers, as a preparation well worth investigation.

PREVIOUS CLINICAL WORK

The first clinical paper presented on crystalline trypsin pertained to the significant value of its intrapleural administration in the sterilization of the disease process and reexpansion of the lung in selected cases of tuberculous and nontuberculous fibrinopurulent empyema.[1] This was followed shortly by articles [2] on the use of the enzyme in the local therapy of many suppurative and necrotic lesions, such as grossly contaminated amputation stumps, subcutaneous hematomas, chronic osteomyelitis, diabetic gangrene, slough wounds after failure of skin grafts, and decubitus and varicose ulcers. The use of trypsin by inhalation was commented on by one of us (L. U.),[3] Roettig and co-workers,[4] and Limber and co-workers [5]; the latter reported on studies undertaken in patients with active pulmonary tuberculosis who had tenacious sputum as well as in patients who had other conditions in which the high viscosity of the sputum presented a problem. Limber and co-workers [5] stated that "In vitro 50,000 units of crystalline trypsin produces a dramatically rapid liquefaction in 25 cc. samples of thick sputum obtained from patients with active pulmonary tuberculosis." This lysis was reflected by a decline in the measured sputum viscosity. Rabbits were also given trypsin in aerosol form and showed no marked histological deviation from the normal appearance of the tracheobronchial tree and lung parenchyma. These authors concluded that "Aerosol trypsin is relatively nontoxic, harmless to respiratory tissue, and does not impede ciliary action."

SELECTION OF CASES

The vigorous fibrinolytic properties of crystalline trypsin, plus its ability to cause digestion of respiratory mucin, indicated that the preparation should be of value in the treatment of disorders of the bronchial tree associated with hypersecretion and accumulation of fibrinomucinous sputum. Thus, this study, conducted both in the hospital and in the office, included a varied group of respiratory conditions, such as bronchial asthma and emphysema that had not responded to usual therapy, bronchiectasis, infectious bronchitis and pneumonitis, acute atelectasis, and recently some work with bulbar poliomyelitis.

ADMINISTRATION

Earlier in this study 125,000 to 250,000 units of aerosol trypsin was given routinely to all patients; however, because of frequent hoarseness at that time the initial dose is now 75,000 units dissolved in 1.5 cc. of the aerosol trypsin diluent (Sorensen's phosphate buffer solution). The first follow-up dose consists of 100,000 units in 2 cc. of the diluent, which is then increased to 125,000 units in 2.5 to 3 cc. of the diluent. It has been observed that 50,000 units of trypsin dissolved in each cubic centimeter of the diluent provides a very satisfactory concentration for clinical results. When larger amounts of the enzyme are dissolved in too little diluent, the solution is viscid, it is apt to clog the baffle tubing of the nebulizer, and untoward reactions are more frequent. It should be mentioned that early in the study when hoarseness was not infrequent and when the initial dose was 125,000 units or more, the inhalations were probably given too rapidly and little stress was given to thorough rinsing of the mouth. Inhalations wherever possible are given every day or two, and the total number of administrations per patient has so far ranged from one to eight.

Before the inhalation, the patient is usually given 0.25 cc. of a 1:1000 solution of epinephrine combined with 0.75 cc. of a soluble antihistamine, such as methapyrilene (Histadyl) hydrochloride or diphenhydramine (Benadryl) hydrochloride. These drugs dilate the bronchi and bronchioles, and the antihistamine possibly reduces the incidence of hoarseness and dyspnea. The "mask" method of aerosolization is used, which consists of rubber tubing extending from the oxygen tank to a DeVilbiss no. 40 glass nebulizer or a Vaponefrin plastic nebulizer. The latter nebulizer is attached directly to a BLB mask rebreathing bag apparatus, whereas when using the DeVilbiss nebulizer a "threaded connector" * covered with a short section of rubber Penrose tubing must be attached to the mask rebreathing bag apparatus. After placing aerosol trypsin in the nebulizer, the mask is strapped to the face with crevices being closed with cotton or moist gauze to prevent escape of the enzyme, and moist gauze dressings are placed over the patient's eyes. Usually 15 to 20 minutes are required to nebulize 2.5 cc. of trypsin solution when using a flow rate of 4 to 6 liters of oxygen per minute.

In addition to the "mask" method, nebulizations may be given by the direct method using oxygen, the direct method using compressed air, or the direct method using a hand pump. The direct method using oxygen consists of rubber tubing extending from the oxygen tank to a glass Y-tube. The latter is connected by rubber tubing to a DeVilbiss or a Vaponefrin nebulizer, which is held between the teeth. During inspiration the open end of the Y-tube is occluded with the thumb to direct the flow of oxygen through the nebulizer. The direct method using compressed air consists of rubber tubing from the compressed air source to a glass Y-tube. The latter is connected by rubber tubing to a DeVilbiss or a Vaponefrin nebulizer. The direct method using a hand pump consists of a DeVilbiss hand pump, rubber tubing, and a nebulizer (combination 740). The hand pump may be operated by either the patient or another person.

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* The Oxygen Equipment and Service Company of Chicago makes the threaded connector 6b for the BLB mask and the threaded connector 6c for the O.E.M. mask.

In order to avoid nasal or oral irritation, patients are advised to inhale through the mouth and exhale through the nose during administration of the aerosol and, immediately after discontinuation of the treatment, to blow the nose and wash out the mouth with water and then to drink a glass of water.

RESULTS

As can be observed in the tables, aerosol trypsin constitutes an ideal agent for removing from the respiratory tract thick sputum that the patient is unable to expel. Generally speaking, the thicker the sputum and the greater the volume the better are the results. In order to determine the efficacy of the inhalations, sputum was collected in a basin after some of the treatments and examined for color, mucoid plugs, and viscosity. It was noted that 14 of 19 patients with bronchiectasis with or without bronchial asthma obtained excellent relief after receiving two to eight inhalations with total dosage varying from 200,000 units to 2 million units. One patient who received 2 million units and one patient who received 1,750,000 units were each given four inhalations followed later by another series of four inhalations. Four of the five patients with acute atelectasis had excellent results from aerosol trypsin inhalations; it is unfortunate that in the first case aspiration through the bronchoscope was performed before the enzyme was available. Nevertheless, the many rales that were present after bronchoscopy disappeared after aerosol trypsin inhalations. In the last case the patient was in a terminal status before inhalations were begun, and even though he died 14 hours after the first inhalation he coughed up much thick sputum. In the other three patients the atelectatic areas vanished after the inhalations. Despite this small number of patients, it would appear that in acute and in impending atelectasis aerosol trypsin could well be an excellent substitute for bronchoscopic aspirations. It has been noted that in many of our patients inhalations of the enzyme produce a slight tickling sensation of the posterior pharyngeal wall, which stimulates coughing; this occurs even in surgical patients who have refused to cough or in whom coughing has been ineffectual due to postoperative pain. Seven of 11 patients with bronchial asthma plus infectious bronchitis or pneumonitis obtained excellent results. The infectious elements were quickly controlled, although the bronchial asthma did not respond as well. In paroxysmal bronchial asthma, aerosol trypsin produced excellent results in four patients (one was a repeat treatment on second admission), good results in one, and no results in two. These comparatively good results contrast rather sharply with the mediocre effects obtained with the use of the enzyme in chronic bronchial asthma associated with more or less emphysema. In this latter group of patients excellent relief was secured in only 5 of 31 patients, with good benefit in 9 patients, and no benefit in 17.

REPORT OF CASES

CASE 1.—A white woman, aged 45, with bronchiectasis was admitted to the hospital May 17, 1952, because of increased dyspnea for the past month, fever, and bubbling rales. Bronchograms revealed a mild cylindrical and saccular bronchiectasis of the lower lobes of both lungs and of the lingular division of the upper lobe of the left lung. A consultant surgeon advised against lobectomy. On the fifth hospital day 250,000 units of aerosol trypsin was given. Within three hours the patient filled an emesis basin with tenacious sputum. The next morning the temperature, which had been up to 101.8 F, was normal for the first time since admission, and remained normal until her discharge six days later. The daily sputum volume while she was in the hospital decreased from 100 cc. down to 15 to 20 cc., and rales greatly diminished. She received three aerosol inhalations totaling 750,000 units. In October, 1952, wheezing and increased expectoration were brought on by a cold. Excellent results were again obtained with a series of three inhalations, each consisting of 125,000 units of aerosol trypsin. This patient will probably need aerosol therapy from time to time.

CASE 2.—A white man, aged 49, had hypostatic pneumonia with atelectasis on the third day following a gastric resection. His morning oral temperature was 103 F, he was slightly cyanotic, and breath sounds were absent in the lower lobe of the left lung; because of pain he would not cough. Roentgenograms confirmed the diagnosis of atelectasis. A single dose consisting of 500,000 units of aerosol trypsin in 7 cc. of Sorensen's phosphate buffer solution (trypsin diluent) was given by aerosol during a period of 40 minutes. The patient coughed during the entire inhalation, and within 30 minutes following termination of treatment filled an emesis basin with thick yellow-green mucus, and mucous plugs. His color improved remarkably, and a roentgenogram taken seven hours later with a portable x-ray machine revealed no evidence of atelectasis, although some density was still present.

TABLE 1.—*Results Obtained with Aerosol Trypsin in Seventy-Three Cases*

Diagnosis	No. of Cases	Results		
		Excellent	Good	None
Bronchiectasis, with or without bronchial asthma	19	14	4	1
Acute atelectasis	5	4	1	..
Bronchial asthma with infectious bronchitis or pneumonitis	11	7	4	..
Paroxysmal bronchial asthma	7	4	1	2
Chronic bronchial asthma with emphysema	31	5	9	17
Total	73	34	19	20
Addendum: Bulbar poliomyelitis with tracheotomy	8	5	3	..

CASE 3.—A white man, aged 56, had pulmonary disease for five years and was admitted to the hospital acutely ill, with marked dyspnea, orthopnea, and wheezing. Roentgenograms revealed marked bilateral infiltration with a suggestion of bronchiectasis, emphysema, and some fluid at the bases of both lungs. Following the administration of 0.5 cc. of 1:1,000 epinephrine, the patient was given 125,000 units of aerosol trypsin. Within one hour he coughed up 150 cc. of thick tenacious sputum containing many plugs. That night he slept well for the first time in three weeks, without dyspnea or orthopnea. On the following day, after the use of 250,000 units, the patient expectorated twice as much sputum. Transient hoarseness developed three hours after the aerosol was given. Roentgenograms taken three days later revealed dramatic clearing of the pulmonary densities. On this day two inhalations, each consisting of 250,000 units, were followed with expectoration of 250 cc. of sputum. The clinical picture continued to improve, the vital capacity increased from 33% to 90% of normal, and he was able to walk up and down stairs without discomfort. The patient was discharged on the 10th hospital day and on readmission for a check-up three months later was in good health. This patient also received injections of penicillin, and credit for his remarkable improvement must be shared by both procedures.

CASE 4.—A white woman, aged 44, was admitted to the hospital with a diagnosis of paroxysmal bronchial asthma. She received four inhalations of 250,000 units each. After each administration several mucous plugs were coughed up, and the clinical picture improved daily. After the first inhalation, a transient rash appeared about the margins of the mouth. Three months later when readmitted to the hospital, similar inhalations gave similar excellent results.

CASE 5.—A white housewife, aged 64, was admitted to the hospital with chronic asthma, emphysema, and mild diabetes. She received three inhalations of aerosol trypsin (125,000, 75,000, and 100,000 units) over a period of seven days. There was no appreciable increase in sputum, and wheezing continued.

COMMENT

On the basis of the aforementioned data it is obvious that aerosol trypsin gives best results in patients with thick or copious sputum such as occurs in bronchiectasis or in acute atelectasis. Favorable results are also obtained in paroxysmal bronchial asthma and in patients with both bronchial asthma and pulmonary infections. The poorest results are in those with chronic bronchial asthma associated with emphysema. The amount of sputum induced by aerosol trypsin immediately following inhalations varied from a few cubic centimeters to as much as three emesis basins full of purulent material. As a corollary to the amount of expectoration, the chest findings are proportionately changed. In those patients who have profuse expectoration and bubbling rales, the dyspnea, wheezing, and cough usually decrease and rales disappear or are lessened. Aerosol trypsin inhalations do not constitute a cure; however, they provide temporary relief to many patients with respiratory disease. When sputum again accumulates, aerosol trypsin should be readministered; good results can again be expected.

TABLE 2.—*Untoward Reactions Observed with 270 Trypsin Aerosol Inhalations in 73 Patients*

Transient hoarseness	14
Increased asthma	4
Rash about lips	1
Nausea and vomiting	1
Total reactions	20

Transient hoarseness occurred in 14 of 73 patients in whom a total of 270 inhalations were given (table 2); however, as studies proceeded, it was observed that the degree and incidence of hoarseness were considerably diminished by administering inhalations more slowly, by giving smaller initial doses, and by having patients wash out their mouths with water after each inhalation. Of the 14 patients with transient hoarseness, the reaction was severe in 3 but disappeared in a few days; some patients received additional inhalations with no recurrence of hoarseness.

In the latter part of our study each patient received 0.25 cc. of 1:1000 epinephrine, and 0.75 to 1.0 cc. of an antihistaminic preparation such as methapyrilene hydrochloride or diphenhydramine hydrochloride 15 to 30 minutes prior to aerosolization. The administration of these drugs probably increases the caliber of the bronchial tree to such a degree that aerosol trypsin reaches a larger area. Furthermore, it is possible that these drugs may have contributed to the lower incidence of hoarseness noted in the latter part of our study.

A temporary skin rash was observed around the margins of the lips in one patient, increased difficulty in breathing in four patients, and caused nausea and vomiting in one patient when the aerosol was given. The latter patient expectorated large amounts of sputum and obtained good therapeutic results. There was no evidence of sensitivity in any of the patients, not even in those patients in whom therapy was resumed after having been discontinued for long intervals. One of the medical technologists has some burning of the eyes and rawness of the throat when administering the aerosol, and another technologist, who is allergic, has transient increase in coughing and rhinitis when not wearing a gauze mask.

SUMMARY AND CONCLUSIONS

Seventy-three patients with respiratory conditions with or without thick, viscous sputum were treated with a naturally occurring body enzyme—trypsin—in aerosol form. This enzyme, which is nontoxic and does not affect living tissue, lessens the viscosity of the sputum.

From the data obtained we believe the following conclusions may be drawn: 1. Inhalations of aerosol trypsin are extremely effective in ridding the upper part of the respiratory tract of thick sputum that the patient is unable to expectorate. 2. Excellent results were obtained in most patients with bronchiectasis, acute atelectasis, and bronchial asthma complicated with bronchitis or pneumonitis; good results were secured in paroxysmal bronchial asthma. We strongly recommend aerosol trypsin in these cases. The majority of patients with chronic bronchial asthma and emphysema received little or no relief, although a few were benefited. 3. Aerosol trypsin is a safe preparation to administer, and, when given in the manner used in the latter part of the present study, hoarseness, the only troublesome side-effect, became much less frequent.

ADDENDUM

With the loss of natural humidifying processes in the patient who has a tracheotomy, especially when he is in a respirator because of respiratory failure from acute bulbar poliomyelitis, dried respiratory secretions present one of the most difficult hurdles in management. The commonest respiratory disease found in these patients at autopsy is probably atelectasis, due partially to the passive activity of the iron lung and partially to mucoid plugs that occlude the bronchi and larger bronchioles. The poliomyelitis patients mentioned in table 1 are but a small number of those who received trypsin inhalations at several Chicago hospitals during the 1952 epidemic. Recently, several articles have appeared on the use of trypsin in selected poliomyelitis patients.[6]

The use of aerosol trypsin in the patient who had undergone a tracheotomy was of necessity different from the aforementioned technique. The DeVilbiss no. 40 nebulizer was used, and a small length of rubber tubing was attached to the mouth of the nebulizer, with the other end of the rubber tubing resting in the cannula of the tracheotomy tube. A flow of 6 or 7 liters per minute of oxygen was passed through the nebulizer. The patient was placed alternately on each side and on his back. One half to one hour after completion of the inhalation, the patient was placed in extreme Trendelenberg position, and tracheobronchial aspiration was done with a long suction catheter. During the aspiration, the patient was again turned from side to side to help postural drainage.

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CASE 6.—A white woman, aged 28, was admitted to the hospital with acute bulbar poliomyelitis. She had undergone tracheotomy and had been in a respirator for 36 hours prior to trypsin inhalations. It was believed that the patient's airway was clear, since only a small amount of mucus could be suctioned through the trachea; however, during this period the patient became progressively more cyanotic, despite the fact that the respirator was in good working order. The patient was unresponsive immediately prior to and during the early part of the inhalation of 250,000 units of trypsin. The enzyme was nebulized directly into the trachea, and during the administration she was rotated from side to side. One half hour after completion of treatment, the patient was placed in extreme Trendelenberg position and tracheobronchial aspiration was necessary for the next 70 minutes to remove all the mucus that drained into the trachea. The patient was greatly improved.

Aerosol trypsin may become an important procedure in the management of patients who undergo tracheotomies, especially in those with acute bulbar poliomyelitis.

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HYPERVENTILATION AND PSEUDOHYPOGLYCEMIC REACTIONS IN DIABETES MELLITUS

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Reactions that usually are regarded as hypoglycemic in origin quite frequently complicate the treatment of diabetic patients receiving insulin. When these are relieved by simple alteration in diet or insulin dosage, they do not become a matter of undue concern to either the patient or the physician. On the other hand, when they fail to be controlled satisfactorily by such measures, their management presents a perplexing problem. The lack of correlation that may occur between the clinical manifestations of reactions and the blood glucose level [1] adds further to the confusion.

Reactions of the latter type—where characteristic symptoms occur in the presence of normoglycemia or hyperglycemia—have been referred to as pseudohypoglycemic reactions.[2] The mechanism for these is not completely understood. Most investigators have sought to relate them to the physiology of diabetes mellitus and have postulated that they are due to some disturbance in the availability, transportation, or utilization of carbohydrate by the brain.[3] Others, however, have presented evidence that reactions of this type may be caused by factors entirely unrelated to diabetes. In 1948 Fabrykant and Pacella reported on seven labile diabetic patients who had frequent pseudohypoglycemic reactions.[2] Because six of these subjects had borderline or abnormal electroencephalograms and three improved with anticonvulsant therapy, it was proposed that electrocerebral dysfunction was the basis for their reactions. (No explanation was offered for those of the seventh patient, who had a normal electroencephalogram and was unimproved by six weeks of Mesantoin [3-methyl-5,5-phenylethyl hydantoin] therapy.)

In the course of a study of the emotional status of a group of diabetic patients, the frequency with which symptoms of hypoglycemic reactions appeared in those who had excessive anxiety was striking. Also, an intimate temporal relationship between such symptoms and anxiety-provoking situations was apparent. When it was established that many of these reactions were of the pseudohypoglycemic type and none of the patients had significant electroencephalographic abnormalities, it seemed possible that some circumstance related to anxiety might be responsible for them. It is interesting that in 1936 Daniels [4] pointed out the similarity between the clinical manifestations of hyperinsulinism and "anxiety neurosis" and subsequently Fabrykant and Pacella [5] commented upon the resemblance of spontaneous hypoglycemia and "hysteria." No efforts were made to elucidate these clinical relationships, however.

The precipitation of hypoglycemia (as well as hyperglycemia) by emotional stress in diabetic patients has been reported by several investigators.[6] Although such observations may pertain to reactions associated with hypoglycemia, they do not provide evidence regarding the possible relevance of emotions to reactions unaccompanied by abnormal depression of blood glucose.

Anxiety has been noted to be a common and prominent component of the personality patterns of diabetic patients.[7] It is well recognized that anxiety is accompanied by physical manifestations that vary widely in their nature and severity. One of these is hyperventilation, which may produce alarming and occasionally incapacitating symptoms. The frequency with which overbreathing occurs in various types of emotional disorders has led to the recognition of the "hyperventilation syndrome" as a clinical entity.[8] As shown in table 1, a comparison of the usual symptoms resulting from hyperventilation with those accompanying mild to moderate hypoglycemia shows a remarkable degree of similarity. In view of the foregoing considerations, the possibility that emotionally induced hyperventilation in certain diabetic patients might be the mechanism responsible for their nonhypoglycemic reactions seemed worthy of investigation.

METHODS AND MATERIALS

All diabetic patients admitted to the medical service of the university hospitals during a 12 month period who were between the ages of 21 and 50 years and who complained of frequent "insulin reactions" were studied. For the purpose of this investigation, however, those whose reactions always were accompanied by hypoglycemia and those who had proved cerebral dysrhythmia (three

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Owing to lack of space, the bibliographic references have been omitted from THE JOURNAL and will be included in the authors' reprints.

patients) were excluded. Each of the remaining patients had a detailed evaluation by a member of the section of psychosomatic medicine and a social service interview, in addition to the usual medical history, physical examination, and appropriate laboratory studies.

During psychosomatic consultation a comprehensive description of each person's "insulin reactions" was recorded. Later in the interview, with the patient in the sitting position, a hyperventilation test (deep respiration at a rate of approximately 30 per minute for two minutes) was carried out. Throughout the course of this test a careful appraisal was made of objective and subjective symptoms. Finally, the patient's description of his "insulin reactions" and his response to hyperventilation were compared.

While hospitalized, all of the patients in this series had daily fasting blood glucose determinations (Folin-Wu). In many instances, blood glucose levels were obtained several times daily. In addition, an effort was made to take blood specimens on the appearance of symptoms suggesting hypoglycemia and before glucose was given. (Blood glucose levels below 70 mg. per 100 cc. were considered hypoglycemic.) Each patient had one or more electroencephalograms (Gilson, eight channel instrument). The terminal portions of the electroencephalograms were obtained during three minutes of hyperventilation, usually with the patient in the sitting position.

TABLE 1.—*Comparison of the Usual Symptoms and Signs of Hyperventilation and Hypoglycemia*

Hyperventilation	Hypoglycemia
Mild Manifestations	
Dizziness	Dizziness
Apprehension	Apprehension
Weakness and fatigue	Weakness and fatigue
Paresthesias (extremities and face)	Paresthesias (extremities and face)
Palpitation and tachycardia	Palpitation and tachycardia
Sweating (flushing and pallor)	Sweating (pallor)
Disturbed vision (blurring)	Disturbed vision (blurring, diplopia)
Tremors	Tremors—trembling sensations
Headache	Hunger and headache
Nausea and "gagging"	Nausea
Shortness of breath	Vomiting
Severe Manifestations	
Panic and hysterical reactions	Apathy and confusion
Muscular hyperirritability (tetany)	Incoordination and ataxia
Syncope	Unconsciousness and convulsions

RESULTS

As presented in table 2, 14 patients (11 men and three women) ranging in age from 28 to 50 years (average, 37 years) were included in this study. With one exception, all were "unstable" diabetics who received insulin in doses of 20 to 70 units daily. Two patients were considered as having "brittle," four severe, and seven moderately severe diabetes mellitus. The remaining subject had mild diabetes that did not require the use of insulin for metabolic control. The duration of diabetes in this group ranged from 3 months to 21 years (average, 9 years). All of the patients had a recent history of frequent (daily to twice monthly) reactions that were attributed to hypoglycemia. During hospitalization 11 of the group had an aggregate of 60 such reactions. The vast majority of these were considered to be "mild" in that they were manifested only by feelings of weakness, dizziness, sweating, nervousness, and/or hunger. Five reactions occurred that were "severe." These were accompanied by apathy, confusion, unconsciousness, and/or convulsions.

Without exception, each of the patients in the series was found to have personality features and emotional patterns regarded as characteristic of patients with diabetes mellitus and similar to those described by Daniels[6a] and Hinkle and associates.[6c] Excessive anxiety was discernible in all of them. Furthermore, their diabetes had become evident clinically in the wake of some particularly stressful life situation, and the subsequent course of the disease seemingly had been influenced by the instability of their emotional reactions.

Correlation of Blood Glucose Levels with Clinical Symptoms of Hypoglycemia.—During 27 of the 60 reactions that occurred, blood samples for glucose determination were drawn before therapy was instituted. Blood glucose levels were found to be normal or hyperglycemic (range from 79 mg. per 100 cc. to 274 mg. per 100 cc.) in 16 and distinctly hypoglycemic (range from 60 to 40 mg. per 100 cc.) in 11. Included in the latter group were the five "severe" insulin reactions. In contrast to the foregoing, it was repeatedly demonstrated that blood glucose levels obtained at times when these patients were symptom-free were in the hypoglycemic range or, as was true in one case, were less than the levels associated with their reactions.

Response to Hyperventilation.—As shown in table 3, all of the 14 patients were found to be hyper-reactive to hyperventilation, i. e., moderate to severe symptoms occurred with overbreathing for two minutes or less. It is noteworthy that, in four of them, hyperventilation produced such an effect within one minute and, in one instance, this occurred with merely "six deep breaths."

In eight patients (including the five who were markedly sensitive to hyperventilation), overbreathing produced symptoms identical to those of their usual reactions. In the other six their hyperventilation symptomatology was regarded as "similar" to that which characterized their reactions.

Electroencephalograms.—The electroencephalographic records of eight of the patients showed low voltage, fast activity; two showed 7 to 9 per second waves in all leads; and four had 10 to 12 per second (alpha) activity. All were interpreted as being within normal limits. In only one instance was there alteration in the electroencephalographic pattern with three minutes of hyperventilation. This occurred in one of the 10 to 12 per second records (case 12) and consisted of slowing of the waves to five per second with a build-up in amplitude to 200 mv. (grade 1.5) during the period of overbreathing.

COMMENT

The data presented show that in certain diabetic patients, reactions simulating mild to moderate hypoglycemia occurred as a result of hyperventilation. Thus, hyperventilation as well as cerebral dysrhythmia pro-

vides an explanation for pseudohypoglycemic reactions occurring in diabetes mellitus.

Although the electroencephalograms of the patients in this series were consistently within normal limits, it is known that hyperventilation will uncover or potentiate otherwise unrecognized cerebral dysrhythmias.[9] It also has been reported that the effects of hyperventilation are augmented in the presence of hypoglycemia.[10] It is entirely possible, therefore, that hyperventilation may have broader ramifications as a mechanism of symptom production in diabetes than merely as an alternative basis for reactions operating in the absence of hypoglycemia and electrocerebral dysfunction.

The hyperventilation syndrome and its diversified symptomatology are recognized readily in the psychoneurotic person who has excessive anxiety. While the presence of anxiety reactions and other psychoneurotic disorders has been emphasized in diabetes mellitus, the occurrence of the hyperventilation syndrome has not. Fortunately, it is a simple matter to test a patient's response to hyperventilation. If typical symptoms of a "reaction" are reproduced by such a test, the physician is afforded a clue that further evaluation of the patient's emotions and their relationship to the course of his diabetes is in order. Obviously, the successful management of such diabetic patients entails appropriate psychotherapy and correction of their faulty breathing pattern under stress, in addition to the usual medical measures.

Unquestionably, most reactions in diabetic patients are hypoglycemic and likewise most are controlled effectively by manipulating the diet and/or insulin dosage. This is not true of all patients suffering from diabetes nor of all

TABLE 2.—*Summary of Data Relating to Diabetes and Pseudohypoglycemic Reactions in the Fourteen Cases Studied**

Patient	Age, Yr.	Sex	Severity of Diabetes	Duration of Diabetes, Yr.	Type and Dose of Insulin, Units	Blood Glucose Levels with "Reactions" Mg./100 Cc.		Blood Glucose Levels without "Reactions" Mg./100 Cc.
						Hypoglycemia	Pseudohypoglycemia	
1	33	M	Brittle	21	PZI, 55	57	99	59, 63, 69
2	44	M	Severe	11	2:1, 60	45, 45, 50	206	45, 50, 57, 60
3	30	M	Severe	17	NPH, 55	42	181	59, 69
4	35	M	Brittle	10	2:1, 60	..	79, 93	50, 53, 57, 59, 67
5	33	M	Severe	12	NPH, 60	No reactions in hospital		44, 57
6	31	M	Severe	8	NPH, 70	49	258	43
7	28	M	Moderate	1	2:1, 44	53	107, 112 114, 156	54, 59
8	36	M	Moderate	13	NPH, 40	..	121	42, 44, 48, 63
9	29	M	Moderate	7	PZI, 45	No reactions in hospital		63, 69
10	42	M	Moderate	15	NPH, 35	No blood drawn with reactions		49, 54, 55
11	50	M	Moderate	½	PZI, 20	49	80	65, 65, 67
12	39	F	Moderate	2	PZI, 45	40, 45, 60	91, 274	.....
13	33	F	Moderate	10	NPH, 45	No reactions in hospital		57
14	48	F	Mild	9	None	..	141, 143	126, 137

* None of the patients had electroencephalographic abnormalities.

TABLE 3.—*Comparison of Symptoms of "Insulin Reactions" and Hyperventilation in Fourteen Diabetic Patients*

Patient	Symptoms and Signs of Typical Insulin Reactions	Symptoms and Signs on Hyperventilation Test	Comparison
1	Dizziness, weakness, nervousness, shakiness, sweating, numbness, "shaking in the stomach"	Dizziness, weakness, nervousness, tremulousness, sweating, paresthesias, "shaking in the stomach"	Identical
2	Dizziness, weakness, shakiness, sweating	Dizziness, weakness, tremulousness, flushing *	Identical
3	Dizziness, weakness, shakiness, sweating	Dizziness, weakness, tremulousness, sweating *	Identical
4	Weakness, nervousness, palpitation, "short of breath," "loss of control"	Weakness, fatigue, tremulousness, palpitation, dyspnea	Similar
5	Weakness, dizziness, sweating, numbness, nervousness, "hazy" feeling	Weakness, dizziness, paresthesias, marked apprehension	Similar
6	Weakness, dizziness, palpitation, "hungry feeling"	Weakness, dizziness, palpitation, "dryness"	Similar
7	Dizziness, weakness, "blurring vision," "fullness of stomach," nervousness	Dizziness, weakness, diplopia, "upset stomach," marked apprehension †	Identical
8	Nervousness, sweating, dizziness, "staggering"	Marked apprehension, flushing, dizziness, tremulousness	Similar
9	Dizziness, weakneses, sweating, shakiness	Dizziness, weakness, tremulousness	Similar
10	Dizziness, weakness, shakiness	Dizziness, weakness, tremulousness, anxiety *	Identical
11	"Pressure in head," palpitation, dizziness, shakiness, sweating, weakness	"Pressure in head," palpitation, dizziness, tremulousness, flushing, weakness *	Identical
12	Sweating, weakness, faintness	Flushing, weakness, faintness	Identical
13	Weakness, faintness, nervousness	Weakness, apprehension, dizziness, palpitation	Similar
14	Weakness, nervousness, shakiness, faintness	Weakness, apprehension, tremulousness, faintness	Identical

* These patients were hyper-reactive to one minute of hyperventilation.
† This patient was hyper-reactive to "six deep breaths."

reactions, however. Other causes for similar symptoms exist. When these are present, it is understandable why efforts directed solely at the regulation of carbohydrate metabolism prove ineffective in their control.

SUMMARY AND CONCLUSIONS

Detailed study of 14 diabetic patients who were having frequent "insulin reactions" revealed the following facts: 1. Reactions that were not accompanied by hypoglycemia occurred quite commonly in this group. 2. All of the patients were excessively anxious and also were hyper-reactive to two minutes of hyperventilation. 3. The symptoms incurred by overbreathing reproduced in these patients their typical symptoms of "insulin reactions." 4. None of the patients had electroencephalographic evidence of cerebral dysrhythmia (even with hyperventilation).

It is concluded that, when the hyperventilation syndrome occurs in anxious diabetic patients, it can produce symptoms that simulate, and thus are easily misinterpreted as, true insulin reactions. With the recognition of this role of hyperventilation and with institution of appropriate psychotherapy for its correction, the physician can be assured of more successful management in certain of his unstable diabetic patients.

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THE PRESENT STATUS OF PLASMA EXPANDERS

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The term "blood substitute," used extensively during World War I and at the beginning of World War II, has been abandoned, since it is agreed that there is no real substitute for blood either in content or in function. In addition, the use of this term is misleading, especially to the public, raising the question as to the necessity for contributions of blood for military and civil defense use or even for friends and relatives. Actually there is no substitute for blood plasma, but certain macromolecular colloidal solutions possessing some of the physical properties of plasma are capable of maintaining the circulating blood volume by virtue of their oncotic pressure, which attracts interstitial fluids into the blood vascular system. The large molecular size prevents their rapid escape into the tissues or through the kidneys until the blood volume has been restored to normal. The term "plasma expander" is now used by the National Research Council and seems the logical name for this group of substances.

The ideal characteristics of these substances have been variously described and defined by many workers. White and Weinstein [1] suggest a plasma expander to be "an agent which will overcome the disparity of the circulatory system that exists in shock, and thus tide a patient over a critical period until such materials as are specifically needed can be given, or the patient can himself manufacture and disseminate enough material to restore his own blood volume."[1] The desirable properties of a plasma expander should include a molecular size large enough for 50% to be retained for 24 hours; an isotonicity, sedimentation rate, osmotic pressure, and viscosity comparable to that of plasma; a molecular structure allowing slow metabolism but not subject to prolonged tissue storage; freedom from pyrogenic, allergic, antigenic, or toxic qualities; and reproducibility and stability.

The earlier experimental and clinical attempts to utilize vegetable colloids having the oncotic properties of plasma, particularly acacia and pectin, proved disappointing chiefly because they produced marked agglutination of the red blood cells in vitro as well as sludging in vivo and prolonged storage in the tissues instead of metabolic degradation. These deficiencies were probably due to the size, shape, and chemical nature of their molecules. Oncley and his associates [2] offer tangible evidence to explain this in physical chemical studies of plasma proteins, showing that their molecular weights vary from 69,000 to over a million and that they are ellipsoid in shape, with only fibrinogen which has a maximum length of 500 A, being in any way comparable to the long chain polysaccharide molecules proposed as plasma expanders. The Council on Pharmacy and Chemistry of the American Medical Association in 1951 reported that so far no blood substitute entirely free from disadvantages has been found. The selection of a foreign material that has the desirable characteristics of human plasma and that could be completely metabolized without producing toxic or allergic reactions would solve the problem.

METHODS OF EVALUATION

In addition to the physical and chemical requirements for plasma expanders, testing in larger animals and man is necessary as regards their effectiveness in hypotensive shock as well as their safety. Their effect in relation to the functional and structural integrity of the vital organs, particularly the lungs, liver, kidneys, and vascular system, must be ascertained.

For determining the relative effectiveness of plasma expanders in the restoration of blood volume after experimental hemorrhage, the methods reported by Bollman, Knutson, and Lundy [3] are apparently simple and

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Based on a paper that was read before the Section on Pathology and Physiology at the 101st Annual Session of the American Medical Association, Chicago, June 10, 1952.

1. White, C. S., and Weinstein, J. J.: Blood Derivatives and Substitutes. Preparation, Storage, Administration and Clinical Results Including a Discussion of Shock Etiology, Physiology, Pathology and Management, Baltimore, Williams and Wilkins Company, 1947, p. 261.

2. Oncley, J. L.; Scatchard, G., and Brown, A.: Physiochemical Characteristics of Certain of the Proteins of Normal Human Plasma, J. Phys. and Colloid Chem. **51**: 184-198, 1947.

3. Bollman, J. L.; Knutson, R. C., and Lundy, J. S.: Symposium on Plasma Volume Expanders in Treatment of Shock: Volemic Substances for Replacement of Blood, A. M. A. Arch. Surg. **63**: 718-727 (Dec.) 1951.

accurate. Rabbits, dogs, and rats were used. The typical experimental procedure included a hemorrhage of 20 ml. per kilogram of rabbit body weight, immediately followed by a blood volume determination using erythrocytes labeled with radioactive phosphorus (P^{32}) and an estimation of the relative erythrocyte-plasma volumes from a hematocrit reading. Immediately after withdrawal of the three minute sample of blood used to determine the volume, the substance used to expand the volume was injected as rapidly as possible into the femoral artery by way of indwelling plastic tubes. Subsequent estimations of blood volume were then made by reverting hematocrit values taken at 15, 30, and 60 minutes as well as at 2, 3, 6, and 24 hour intervals to the original blood volume determination. Using this procedure, these workers show the relative effectiveness of several macromolecular substances in the maintenance of blood volume immediately after replacement and up to 24 hours.

Data [4] relating to the distribution and storage of expanders may be obtained in the case of dextran and polyvinylpyrrolidone when these substances are labeled with radioactive carbon (C^{14}). With other macromolecules as well as with dextran and polyvinylpyrrolidone histological studies are indicated. In prolonged retention they are readily recognized through the presence of the phagocytized material in parenchymal cells, endothelial cells, and especially the reticuloendothelial cells.[5] In addition material escaping into the tissues may produce a foreign body reaction or a granulomatous inflammatory reaction. The use of specific stains for these macromolecules affords additional evidence of their presence.

Experimental methods designed for evaluating the efficacy of a plasma extender in combating marked hypotension usually employ the hemorrhage and replacement technique. The method in which a single massive hemorrhage is continued until respiratory arrest or cessation of bleeding occurs and then the test substitute is employed for immediate replacement has been useful but is scarcely crucial enough for evaluation of hyperoncotic expanders currently being used. Therefore, the animal survival method used by Govier and his associates was our selection. It was employed with the advantage of coincident continuous blood pressure tracings.

Dogs, under light thiopental (Pentothal) anesthesia, were prepared for blood pressure recording from the right femoral artery and for bleeding from the left femoral artery. Intravenous infusions were made through the right femoral vein. The animals were subjected to three massive hemorrhages at 30 minute intervals, which would be fatal if untreated. Accordingly, in the first stage enough blood was removed to cause respiratory arrest, in the second 70% of the amount in the first stage was removed, and in the third 48% of the amount in the first. There was immediate rapid replacement after each bleeding with an equivalent volume of test substance. Blood for hematocrit estimation was drawn during each hemorrhage and 15 minutes after the end of the third infusion. The cannulated vessels were tied off, and the wounds were disinfected and sutured. The animals were considered to have survived the experiments if they lived for 24 hours after the end of the third replacement. As data with this method accumulated, we were impressed with the marked individual variation in the experimental animals. It seemed expedient, therefore, to include another end point for the first hemorrhage as well as that laid down by Govier. In some animals, cessation of blood flow occurred prior to respiratory arrest and so was taken as an end point. In this series, the first massive hemorrhage equaled from 4 to 5% of the body weight. Consequently, 75 to 80% of the blood volume was replaced with plasma expander. At autopsy complete gross and microscopic examination of all tissues was carried out.

DATA

Hueper [6] and others have pointed out that there are three classes of macromolecular substances found worthy of consideration as plasma extenders. These are proteins, including serum albumin, globulin, bovine plasma, and the gelatins; carbohydrates, including gum acacia, glycogen, pectin, dextran, and okra; and the synthetic polymer, polyvinylpyrrolidone.

Proteins as Plasma Expanders.—Gelatin, the incomplete protein derived from the collagen of bones and skin and degraded by several different methods, has been widely used during the last war and is commercially available. The gelatin concentrations in solutions available vary from 3 to 6%, and the viscosities and oncotic pressures vary not only as to the percentage but also according to the amount and type of degradations. Gelatin (5%) supplied by the Upjohn Company has a relative viscosity of 8.12 to 14.0 and an oncotic pressure of 69 to 75 cm. of water at 25 C while that supplied by the Baxter Laboratories (6%) has a relative viscosity of 5.45 and an oncotic pressure of 75 to 80 cm. of water at 25 C. Both of these solutions solidify on refrigeration. These products apparently correspond to the commercial preparation of special gelatin solution, intravenous, which is degraded with heat for shorter periods and has an average molecular size of above 30,000. In 1942, Pauling and his associates [7] prepared gelatin by using glyoxal and hydrogen peroxide to degrade the molecule to a smaller size. The resulting product, oxypolygelatin, has a molecular weight of about 30,000 to 40,000 and does not solidify at temperatures above 5 C. Oxypolygelatin, in 5% solution, has a relative viscosity of 2.25 and an approximate oncotic pressure of 39 to 45 cm. of water at 25 C, both values being somewhat higher than those of plasma. Pulaski [4] has recently mentioned a "fluid" gelatin, prepared by treatment with an aromatic amine that solidifies at 0 to 4 C in 6% solution. This report further states that in "hemorrhagic hypotensive

4. Pulaski, E. J.: Clinical Status of Plasma Substitutes, Chem. & Eng. News **30**: 2187-2189, 1952.

5. Hartman, F. W.: Symposium on Plasma Volume Expanders in Treatment of Shock: Tissue Changes Following the Use of Plasma Substitutes, A. M. A. Arch. Surg. **63**: 728-730 (Dec.) 1951.

6. Hueper, W. C.: Macromolecular Substances as Pathogenic Agents, Arch. Path. **33**: 267-290 (Feb.) 1942. Hueper, W. C.: Experimental Studies in Cardiovascular Pathology: Effects of Intravenous Injections of Solutions of Gum Arabic, Egg Albumin and Gelatin upon the Blood and Organs of Dogs and Rabbits, Am. J. Path. **18**: 895-933 (Sept.) 1942.

7. National Research Council: Conference on Blood Substitutes, edited by D. H. Campbell and others, National Research Bulletin, Washington, 1949, appendix D, p. 73.

shock" the new preparation appears more effective than other gelatins or dextran. This product may be identical or at least similar to the "modified fluid" gelatin reported by Parkins, Perlmutt, and Vars.[8]

In combating hematogenic shock in dogs, the gelatins are effective not only in establishing a prompt rise in blood pressure but also in assuring recovery. Typical data, using plasmoid gelatin as the replacement fluid, are shown in figure 1. In the hemorrhage replacement technique employed, 100% or eight of eight animals survived with 5% plasmoid gelatin; 83% or five of six survived with 6% gelatin; and 67% or four of six survived with 5% oxypolygelatin. This indicates the superiority of 5 and 6% gelatin over 5% oxypolygelatin as a plasma expander.

Tissue changes produced by gelatin solutions consist chiefly of transient swelling of the tubular epithelium of the kidney and temporary storage in the liver and reticuloendothelial system. Recent histological studies on rabbits who received 15 cc. per kilogram every other day for five injections showed a giant cell reaction in the lung (fig. 2*A*).

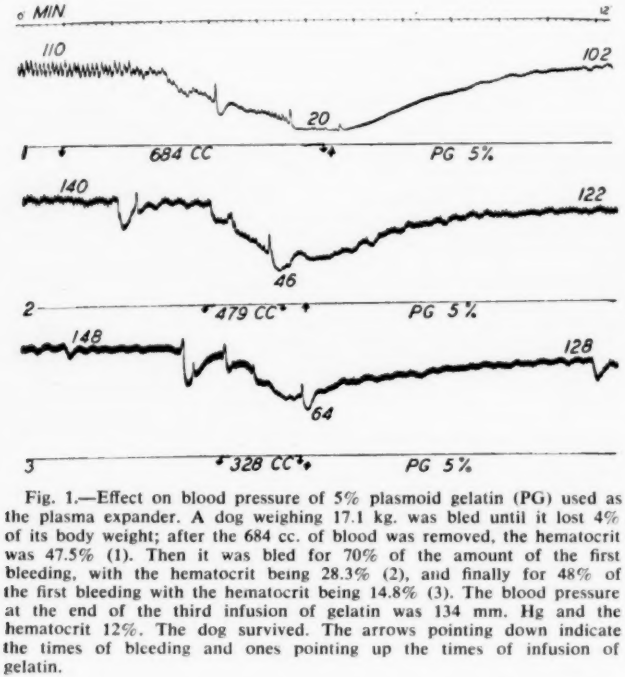

Fig. 1.—Effect on blood pressure of 5% plasmoid gelatin (PG) used as the plasma expander. A dog weighing 17.1 kg. was bled until it lost 4% of its body weight; after the 684 cc. of blood was removed, the hematocrit was 47.5% (1). Then it was bled for 70% of the amount of the first bleeding, with the hematocrit being 28.3% (2), and finally for 48% of the first bleeding with the hematocrit being 14.8% (3). The blood pressure at the end of the third infusion of gelatin was 134 mm. Hg and the hematocrit 12%. The dog survived. The arrows pointing down indicate the times of bleeding and ones pointing up the times of infusion of gelatin.

There is difference of opinion concerning the percentage of gelatin metabolized, but all workers agree that some of it is utilized. The excretion of gelatin by the kidney depends for the most part on the molecular size. As many as 50% of the molecules weighing over 30,000 to 35,000 are reported to be retained for 24 hours.

Carbohydrates as Plasma Expanders.—Dextran, according to Bull,[9] is a biosynthetic polysaccharide composed of glucose units produced by the growth of Leuconostoc mesenteroides in sucrose through enzymatic action. As first precipitated with acetone, dextran appears as a sirupy gum with long chain molecules of such large size (probably at least 1 million) that degradation by acid hydrolysis is necessary to get a substance suitable for intravenous use. Many small molecules also result but the desirable range, about 75,000, can be obtained through fractional precipitation with acetone. Dextran (6%) supplied in limited quantities to us through the National Research Council is a pale straw-colored solution with a viscosity of 3.16 to 3.66 and an oncotic pressure of 65 to 70 cm. of water at 25 C.

Dextran in 6% concentration has excellent characteristics for restoring the blood pressure following hemorrhage. In fact, the blood pressure elevation following three hemorrhages and replacements usually exceeds the blood pressure at the onset of the procedure, as illustrated in figure 3. The survival rate in these experiments with dextran was four of six animals or 67%. Studies in progress on this expander may raise this percentage.

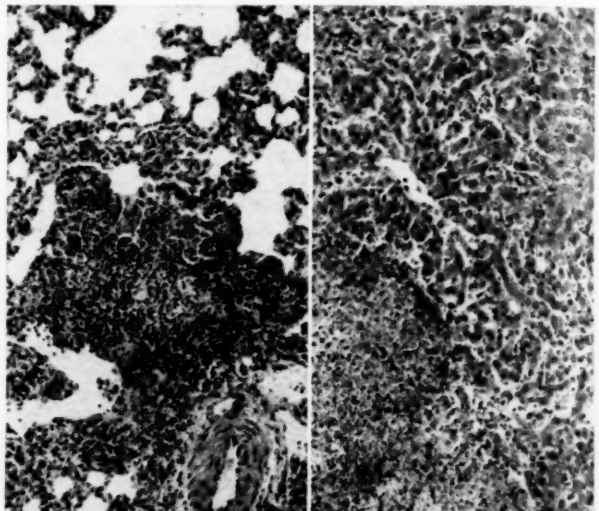

Fig. 2.—*A*, section of lung of rabbit, which was killed after it was given 15 cc. per kilogram of body weight of 5% oxypolygelatin every other day for five injections. Foreign body giant cells and a granuloma can be seen (medium power). *B*, section of liver of rabbit, which was killed after being given 15 cc. per kilogram of 6% dextran every other day for five injections. The liver shows necrosis of the liver cells, foreign body giant cells, and round cell invasion (medium power).

When administered intravenously to mice and rabbits, it is well tolerated. Allergic reactions, as reported by Pulaski [4] in rats and man, were not observed in our mice, rabbits, or dogs. Immature mice receiving 15 cc. per kilogram of a 6% solution three times per week to a maximum of 46 injections continued to develop and to gain weight. Young rabbits averaging 2 kg. in weight who received a comparable amount every other day for five injections showed no gross effects.

Bull and associates,[9] Craig and others,[10] and Pulaski [4] have reported that dextran compares favorably with or

8. Parkins, W. M.; Perlmutt, J. H., and Vars, H. M.: Dextran, Modified Fluid Gelatin and Other Plasma Volume Expanders in Hemorrhaged Dogs, Fed. Proc. **2**: 116-117 (March) 1952.

9. Bull, J. P., and others: Dextran as a Plasma Substitute, Lancet **1**: 134-143 (Jan. 22) 1949.

10. Craig, W. M.; Gray, H. K., and Lundy, J. S.: Symposium on Plasma Volume Expanders in Treatment of Shock: Present Status of Plasma Volume Expanders in the Treatment of Shock: Clinical Results in Surgery, A. M. A. Arch. Surg. **63**: 742-749 (Dec.) 1951.

is actually superior to other currently investigated expanders. Pulaski states that after injection of C^{14}-tagged dextran in the dog, the urine shows 65 to 70% of the radioactivity, with 4 to 6% in the expired CO_2 and 3 to 5% in the viscera at the end of 72 hours. This indicates that at least 25% remains "lost." C^{14}-marked material was found also in the liver, spleen, and lymph nodes. The

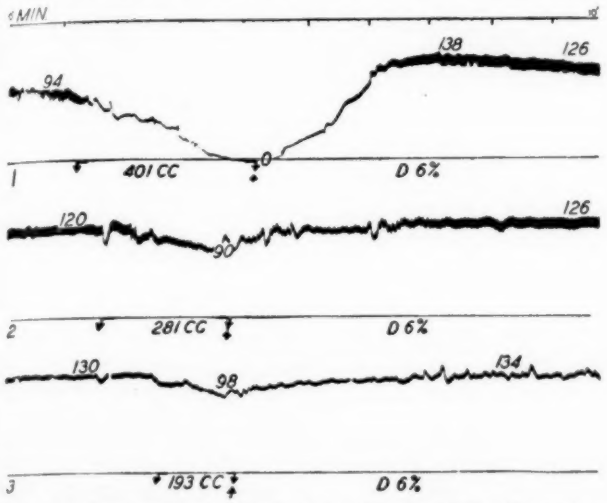

Fig. 3.—Effect on blood pressure of 6% dextran solution (D) used as the plasma expander. A dog weighing 10 kg. was bled until it lost 4% of its body weight; after the 401 cc. of blood was removed, the hematocrit was 50% (1). Then it was bled for 70% of the first bleeding, with the hematocrit being 22.8% (2), and finally for 48% of the first bleeding, with the hematocrit being 10% (3). The blood pressure at completion of the third infusion of dextran was 134 mm. Hg and the hematocrit 9%. The dog survived. The arrows pointing down indicate the times of bleeding and the ones pointing up the times of infusion of dextran.

latter observation corresponds with our histological findings in mice and rabbits. The production of foam cells in the reticuloendothelium of the lymph nodes and in the lungs in mice and focal necrosis of the liver in rabbits was most striking. The pathological findings in the liver are shown in figure 2*B*.

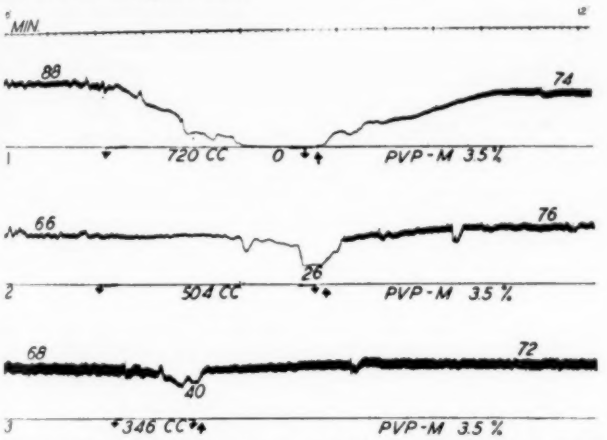

Fig. 4.—Effect on blood pressure of 3.5% polyvinylpyrrolidone (PVP-Macrose) as a plasma expander. A dog weighing 18 kg. was bled until it lost 4% of its body weight; after the 720 cc. of blood had been removed, the hematocrit was 57% (1). Then the animal was bled for 70% of the first bleeding, with the hematocrit being 25% (2), and finally for 48% of the first bleeding, with the hematocrit being 14% (3). At the end of the third infusion of polyvinylpyrrolidone, the blood pressure was 78 mm. Hg and the hematocrit 9%. The dog survived. The arrows pointing down indicate the times blood was withdrawn and those pointing up the times polyvinylpyrrolidone was infused.

Synthetic Polymers as Plasma Expanders.—Polyvinylpyrrolidine (PVP) is a colloid produced through the chemical combination of formaldehyde and acetylene. Weese [11] first tried it as a plasma extender in Germany during the last war and many reports of its clinical application have been made. Studies on tissue retention have also been numerous. The imported polyvinylpyrrolidone material used by us was furnished by the General Aniline Corporation. The molecular weight of the 3.5% solution is reported to be approximately 40,000; the viscosity was found to be 2.14 to 2.20, and the oncotic pressure, 33 to 35 cm. H_2O. Another polyvinylpyrrolidone preparation, PVP-Macrose (3.5%), as supplied to us by the Schenley Laboratories, has a higher molecular weight (65,000 to 70,000) than the imported product. The oncotic pressure was found to be 38 to 40 cm. H_2O at 25 C and the relative viscosity, 2.11 to 2.26. Both of these solutions are stable, nontoxic, and nonantigenic in mice and rabbits. Mice tolerate this expander intravenously, but both the rabbit and the dog show immediate reactions unless a preliminary injection is given 24 hours in advance.

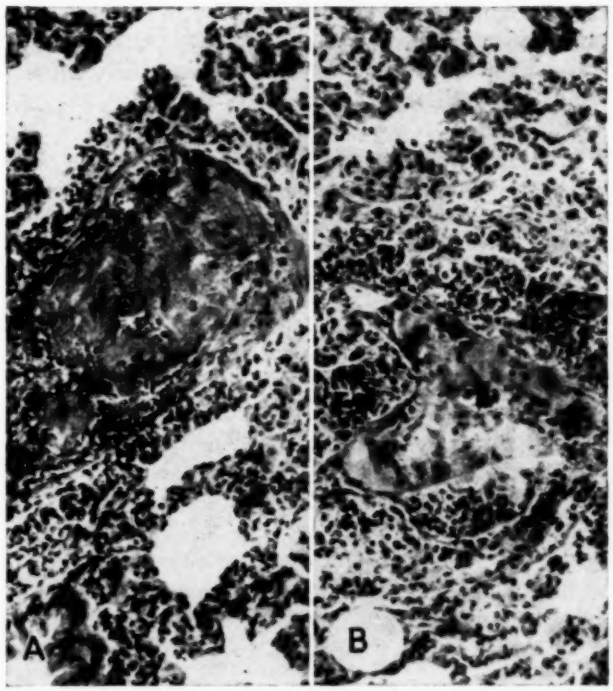

Fig. 5.—*A*, section showing thrombosis in the pulmonary vein of a dog weighing 8.5 kg. that had received 744 cc. of a 3.5% polyvinylpyrrolidone solution (PVP-Macrose) in a hemorrhage-replacement experiment (medium power). *B*, section of lung of rabbit that was killed after being given 15 cc. of 3.5% PVP-Macrose per kilogram of body weight every day for five injections. A foreign body giant cell reaction can be seen (medium power).

In evaluating polyvinylpyrrolidone in the dog by the survival method, one must administer a desensitizing dose (2 to 3 cc. per kilogram) of polyvinylpyrrolidone at least 24 hours prior to the experiment. If this is done, untoward reactions, especially prolonged hypotension, are avoided. A characteristic tracing of blood pressure in a hemorrhage-replacement study with PVP-Macrose is shown in figure 4. Although this polyvinylpyrrolidone as an expander does not create as prompt nor as marked an elevation in blood pressure as do the gelatins and dextran, survival figures are comparable. In our experi-

11. Weese, H.: Indifferente Kolloide in innerer Medizin und Chirurgie, Deutsche med. Wchnschr. **76**: 757-761, 1951.

ence, PVP-Macrose is superior to the imported product in counteracting hemorrhagic hypotension. The imported polyvinylpyrrolidone allowed only a three of six or 50% survival rate, whereas PVP-Macrose brought about recovery in six of seven or 86% of the animals.

Pulaski states that 40 to 60% of injected polyvinylpyrrolidone is excreted unchanged by the kidneys in the first 24 hours. Definite storage can be demonstrated with polyvinylpyrrolidone tagged with I^{131} or C^{14}. In our studies with the General Aniline polyvinylpyrrolidone storage was well marked in the endothelial cells of blood vessels, the reticuloendothelial cells, the liver, and the kidney in the mouse. In the survival studies on dogs, signs of retention were encountered in tissues taken at autopsy. Figure 5*A* depicts a pulmonary vein showing thrombus formation in a dog weighing 8.5 kg. that had received 744 cc. of polyvinylpyrrolidone as blood replacement. Foreign body giant cell reactions were observed in the lungs of rabbits receiving 15 cc. per kilogram every other day for five injections of PVP-Macrose, but retention in the endothelial and reticuloendothelial cells was less striking (fig. 5*B*).

COMMENT

The available plasma expanders have been evaluated as to those characteristics that are required of an effective substitute for plasma. Molecular weight, oncotic pressure, pH, and relative viscosity data are summarized in table 1.

Gelatins, dextran, and polyvinylpyrrolidone have been studied in mice, rabbits, and dogs. Mice and rabbits have been used from the standpoint of tolerance, growth, development, and tissue changes during and after the intravenous injection of these colloids. The effectiveness of these plasma expanders in restoring the blood volume after three hemorrhages is shown by the kymographic

TABLE 1.—*Data Relating to the Characteristics Required of Effective Plasma Expanders*

	Approximate Molecular Weight	Approximate Oncotic Pressure, Cm. H_2O at 25 C	pH Range	Relative Viscosity to H_2O at 20 C
Gelatin, 6%	60,000-80,000	75-80	6.80-7.07	4.62- 5.59
Plasmoid gelatin, 5%	40,000-50,000	69-75	6.58-6.79	8.12-14.00
Oxypolygelatin, 5%	10,000-43,000	39-45	4.98-5.17	1.98- 2.25
Polyvinylpyrrolidone (imported), 3.5%	40,000 (average)	33-35	6.13-7.0	2.14- 2.20
PVP-Macrose, 3.5%	65,000-70,000	38-40	6.63-7.07	2.11- 2.26
Dextran, 6%	31,000-56,000	65-70	5.00-6.22	3.16- 3.66

tracings of the blood pressure. The gelatins seem to give somewhat better immediate and sustained blood pressure responses as well as a higher percentage of survivals. This observation may have its explanation in the greater molecular weights, higher oncotic pressures, and increased relative viscosities of the heat-degraded gelatins.

No immediate toxic or allergic reactions were observed with these colloids in mice or rabbits. Reactions in dogs were seen only with polyvinylpyrrolidone when the recommended preliminary injections were omitted.

Survival data obtained in hemorrhage-replacement experiments on the plasma expanders studied are summarized in table 2. The hyperoncotic properties of 5 to 6% gelatin and dextran establish blood pressures following three hemorrhages that exceed the existing pressure at the time of the first massive hemorrhage. Polyvinyl-

TABLE 2.—*Rate of Survival in Experiments in Which Blood Was Replaced with Plasma Expanders*

Plasma Expander	No. that Survived	Survival Rate, %
NaCl, 0.85%	0 of 7	0
PVP (imported), 3.5%	3 of 6	50
Dextran, 6.0%	4 of 6	67
Oxypolygelatin, 5.0%	4 of 6	67
Gelatin, 6.0%	5 of 6	83
PVP-Macrose, 3.5%	6 of 7	86
Plasmoid gelatin, 5.0%	8 of 8	100

pyrrolidone, with an oncotic pressure only slightly higher than plasma, is less effective in maintaining normotension, yet the survival rate is almost as good.

Tissue retention with foreign body giant cell as well as foam cell formation was observed with the various gelatins as well as the other preparations for the first time in rabbits. This is in agreement with the tissue changes previously reported in mice with pectin, dextran, and polyvinylpyrrolidone. The localization was in the lungs and liver.

CONCLUSIONS

After this second year's work on the experimental use of the plasma expanders, the data support the view that the gelatins are the most promising class of substances used for this purpose. The emergency use of dextran and polyvinylpyrrolidone in limited quantities as well as gelatin is justified in the treatment of shock states. The tissue changes observed should not interfere with function unless greatly exaggerated and multiplied.

Q Fever.—The importance of ticks as a reservoir of *C. burneti* is shown by the large number of species found naturally infected or capable of experimental transmission, their widespread geographical distribution, the profuse multiplication of rickettsiae within infected ticks and the failure to implicate any other group of arthropods. However, ticks have very little relation to human infection. On the other hand, the reservoir of infection represented by cows, sheep and goats is very important as a source of human infection. Infectivity resides particularly in placentae and milk. Human case-to-case infection is on record, but is rare.

The association of "Q" fever patients with the animals from which they were presumably infected shows all degrees of closeness. Some patients were occupationally in immediate contact with animals; some resided near by. Infection was occasionally carried on clothing and very often in dust. Sometimes the association with animals was remote but traceable. Sometimes no association at all could be discovered. The high resistance of *C. burneti* to heat and desiccation allows contaminated material to retain its infectivity for long periods during which it may be transported to a distance. Inhalation is the mode of entry of *C. burneti* into man in the great majority of cases. A small but definite group appears to be due to the ingestion of raw milk. Occasional examples of other portals of entry may be found. . . .—E. H. Derrick, The Epidemiology of "Q" Fever: A Review, *The Medical Journal of Australia*, Feb. 21, 1953.

ORALLY ADMINISTERED HEXAMETHONIUM CHLORIDE IN HYPERTENSION

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Causative factors in the development of hypertension are numerous; however, one common denominator in the hypertensive state appears to be sympathetic predominance over the vasoconstrictor mechanisms responsible for maintaining arterial blood pressure. Today, there are available a number of therapeutic agents that are capable of lowering the blood pressure by "blocking" the flow of nervous impulses over the sympathetic nervous system. The majority of these drugs are impractical for routine use, because of the development of tolerance or the presence of untoward side-effects or because they are destroyed in the gastrointestinal tract and must, therefore, be given parenterally. Despite this fact, great impetus has been given to the search for more effective agents that can be administered orally and that will lower the blood pressure on a long-term basis and thus arrest the progression of the disease. Frequently, original reports on potential hypotensive drugs are enthusiastic, yet, when the drugs are distributed for general use, the results cannot be duplicated. This has been especially true when the preliminary drug evaluation has been carried out with hospitalized patients under the strict control of highly specialized investigative teams. Failure of subsequent investigators and physicians in general office practice to reduplicate the results is due largely to the fact that exact control of the patient's activities and the drug administration cannot be maintained as well on an outpatient basis. It is the purpose of this report to present results on the treatment of hypertension with orally administered hexamethonium chloride, an effective autonomic ganglionic blocking agent. Since these studies were conducted on an outpatient basis, the problems encountered will closely parallel those met in general office practice. The results are compared with those obtained with other currently available hypotensive drugs that have been used in this same clinic under similar circumstances.

METHOD AND MATERIALS

At the start, a group of 98 unselected ambulatory patients who attended the medical and cardiac clinics and 35 private patients were given hexamethonium orally; however, 13 were lost to the study because they moved from the area or because they failed to return to the clinic. All of the remaining 120 patients had blood pressures, as measured in both the supine and upright positions, of 160/100 mm. Hg or greater. They appeared at the clinic at weekly or semiweekly intervals for six weeks to three months before being given the drug. Some of the more seriously ill patients were hospitalized for the induction of drug therapy and were not followed for so long a control period. There were 40 men and 80 women, whose ages ranged from 26 to 71 years. All were subjected to the usual laboratory tests for evaluating patients with hypertension. These included electrocardiogram, chest roentgenogram, eye ground examination, routine urinalysis, urine concentration, phenolsulfonphthalein excretion, urea clearance, and blood urea nitrogen determinations. Following the control periods, during which the patients received only supportive therapy and placebo medication, therapy with the chloride salt of hexamethonium was started, and the patients were followed at weekly or semiweekly intervals as outpatients. The severer the hypertension, the more frequently the patients were seen. When special problems arose, the patients involved were seen in the clinic every day or were hospitalized. During the initial studies some patients were treated with the bromide rather than the chloride salt, but an analysis of the results indicated that there was no difference in the hypotensive response.[1] Because of the potentiality of brominism,[2] the use of the bromide salt was discontinued. The control as well as the follow-up blood pressure determinations were taken in both the supine and upright positions at the time of each visit of the patient to the clinic. This is necessary for adequate evaluation, because the hypotensive response is predominantly orthostatic, which is also true with the use of other ganglionic and adrenergic blocking drugs. The blood pressure was determined by the investigator on each clinic visit as well as by the clinic nurse at the time the patient registered in the clinic and several hours later, just prior to the patient's return home. These multiple observations over a three to four hour period offered an additional opportunity for evaluating variations in blood pressure between doses of the drug. The control supine and upright blood pressure for each patient in the present report was determined by taking the average of all blood pressure observations during the control period in each position. The post-drug blood pressure is the average of the values obtained after the titration period (during which the blood pressure and drug dosage were being stabilized). In addition to the observations on blood pressure, clinical manifestations of excessive hypotension, such as dizziness on standing and excessive weakness during certain parts of the day, were taken into account while adjusting the dose schedule. The initial dose of hexamethonium was usually 250 mg. four times a day, given orally with each meal and at bedtime. Taking the drug with meals was found advisable in most patients, because it decreased the variation in gastrointestinal

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The hexamethonium chloride used in this study was supplied by Chilcott Laboratories, Division of the Maltine Company, Morris Plains, N. J., as Methium, Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y., as Hexameton, and Ciba Pharmaceutical Products, Inc., Summit, N. J., as Esomid.

1. Johnson, I.; Moyer, J. H.; Mills, L. C., and Miller, S. I.: Treatment of Hypertension: Results with Hexamethonium Salts Administered Orally, Texas J. Med. **48**: 331, 1952.

2. Holt, M. C., and Litchfield, J. W.: Bromism on Low Sodium Diets, Letters to the Editor, Lancet **1**: 347, 1951.

absorption of the drug. Also, mealtime and bedtime were good reminders to the patients to take their medicine. Although a more constant blood level of hexamethonium no doubt can be maintained if the drug is administered in smaller doses every three to four hours around the clock, when this technique was followed, most of the patients objected to the routine and were less dependable in taking their medicine than when the drug was given as outlined above. Because of the psychogenic aspects of hypertension and because too much of the patient's attention has already been focused on the disease, such considerations as dose schedule become of utmost importance if therapy is to remain practical over a long period. The dose of hexamethonium was gradually increased in a stepwise fashion until an adequate blood pressure response was obtained or until side-reactions forced discontinuance of use of the drug. One week was allowed between changes in the dose schedule, unless the patient was in the hospital during the titration period. An example of the titration method for establishing the dose schedule is as follows:

	7 A. M.	12 Noon	5 P. M.	10 P. M.
1st week	250 mg.	250 mg.	250 mg.	250 mg.
2nd week	500 mg.	250 mg.	250 mg.	500 mg.
3rd week	500 mg.	500 mg.	500 mg.	500 mg.
4th week	750 mg.	500 mg.	500 mg.	750 mg.

In raising the dose of hexamethonium, the morning dose and that taken before retiring were increased first, since the interval between these two (in which the patient did not receive medication) was greater than at any other time during the 24 hour period. This also helped avoidance of excessive increases in blood concentrations of hexamethonium during the afternoon and early evening. Several patients who showed too much variation in blood pressure between doses were given the drug in smaller amounts more frequently.

RESULTS

Thirteen of the original 133 patients were lost from the study for one reason or another. This does not include any of the patients who were dropped because of prohibitive side-reactions or death. For purposes of analysis, the remaining 120 patients on whom adequate follow-up could be maintained have been divided into three groups, according to the diastolic blood pressure. Group 1 consists of 29 patients with less severe hypertension, in whom the average diastolic pressure during the control period was more than 100 but less than 120 mm. Hg; group 2 consists of 58 patients in whom the control diastolic pressure was more than 120 but less than 140 mm. Hg; and group 3 includes 33 patients with the severest hypertension, in whom the diastolic blood pressure was more than 140 mm. Hg. The patients who failed to respond to treatment were predominantly Negro women. This latter observation probably reflects inability to cooperate with the therapist rather than any variation in pharmacological response to the drug.

Some of the pertinent clinical and vital data on these patients are summarized in table 1. About one-third of the patients had evidence of renal impairment prior to therapy, as indicated in the renal function studies employed. Of the patients in group 1, only 4 of 29 showed evidence of renal involvement, whereas in group 3 (diastolic pressure above 140 mm. Hg) over half showed evidence of impaired renal function. This did not indicate that renal disease preceded the hypertension. More likely the reverse was true in most instances, since patients with frank evidence of acute or chronic nephritis were not included in the study. The blood urea nitrogen level was elevated in 9 instances, and numerous red cells were found in the urine of 22 patients (table 2). Most of these patients fell into group 3, additional evidence of the severity of the disease in this group. Eight patients in group 3 and 12 in group 2 were classified as having malignant hypertension. About one-third of the patients had evidence of congestive heart failure. This had already been treated prior to hexamethonium therapy in most instances. In a few of the patients with less severe failure, no cardiac therapy was inaugurated in order to evaluate the effect of blood pressure reduction alone on the clinical course of heart failure. Thirty-one patients complained of precordial pain prior to therapy. This was typically anginal in type in 15. Three of these patients had previously had myocardial infarction. Three additional patients who had had coronary occlusions had no residual anginal pain. The electrocardiograms during the control periods were interpreted as being abnormal in 92 patients included in the present study. In 48 there was evidence only of left ventricular hypertrophy, whereas in the remaining 44 there was evidence of frank myocardial damage. Cerebrovascular disease was present in 22 patients, as evidenced by previous cerebral arterial occlusions or hemorrhages or by the presence of encephalopathic manifestations.

The blood pressure responses of the three groups of patients are presented in table 3. The period of follow-up after receiving hexamethonium varies from 3 to 18 months. For purposes of evaluating drug tolerance, hypotensive response, and clinical improvement, the patients in each group have been subdivided according to the follow-up period as of the present time, i. e., 3 to 6 months, 6 to 12 months, or 1 year or longer. Table 3 shows the mean blood pressure values for all patients in each group and subgroup who showed a reduction in mean blood pressure of 20 mm. Hg or more as well as the mean values for the unresponsive patients in each group. There was no evidence to indicate that increasing amounts of hexamethonium were required with time to maintain the hypotensive response, that is, that drug tolerance occurred, since the patients who were treated for one year or more did not require more of the drug after this period than patients who had received it for only three months. In looking over individual patients' records, it was observed that a number of patients required more drug per day after one year than they did initially, but just as many required less. There was no obvious answer to account for the variability of drug requirements from time to time; however, it was noted that during periods of increased activity or hot weather the drug requirement decreased. This may represent decreased excretion due to depressed renal function at these times. On the other hand, periods of increased nervous tension usually increased the amount of drug necessary to control the blood pressure. If the blood pressure was reduced excessively, the amount of drug required to maintain the hypotensive response was less than if the

blood pressure was allowed to remain at mildly elevated levels, probably owing to changes in the glomerular filtration rate and variations in the drug excretion rate. Patients in all three groups who were considered unresponsive to the drug received as large as or larger average daily amounts than the responsive patients.

The reduction in blood pressure was greater in the upright position than in the supine. Percentagewise, there was often more of a decrease in systolic than in diastolic blood pressure while standing. In the supine position, the percentile reduction in systolic and diastolic pressure was about equal. Since the drug blocks off the sympathetic innervation to the heart (fig. 1), reflex tachycardia usually did not accompany the reduction in blood pressure. When compared with the control observations, the average blood pressure for patients with severer hypertension (group 3) was lower in those who had been followed for six months to a year than it was in those who had been followed for only three months. This probably reflects greater stability of the blood pressure and better understanding of each patient's problems and idiosyncrasies by both the physician and the patient himself over a longer period.

The initial side-effects associated with hexamethonium therapy were numerous, but in very few instances were they prohibitive or serious enough to cause concern.* This was not the case if the dose of the drug was built up too rapidly and the blood pressure was reduced excessively by overshooting the point at which the dose of the drug was optimal. When this occurred, syncope on standing was almost always seen. At the same time, the patient complained of weakness, dryness of the mouth, blurred vision, and difficulty in defecation. All these improved as

TABLE 1.—*Clinical Data and Incidence of Complications Associated with or Due to Hypertensive Vascular Disease Prior to Therapy*

	Renal Disease		Heart Failure		ECG * Changes		Cerebrovascular Complications		Previous Myocardial Infarction		Precordial Pain		Sex		Race		Average Age
	No.	% †	No.	%	No.	%	No.	%	No.	%	No.	%	Male	Female	Negro	White	
Group 1 (29 patients)																	
Responsive, 25 patients	2	8	10	40	10	40	0	0	2	8	7	28	5	20	12	13	51
Unresponsive, 4 patients	2	50	2	50	1	25	2	50	2	50	2	50	..	4	..	4	55
Group 2 (53 patients)																	
Responsive, 49 patients	18	37	18	37	39	80	11	22	2	4	14	29	21	28	20	29	48
Unresponsive, 9 patients	3	33	5	56	9	100	5	56	..	..	5	56	3	6	8	4	51
Group 3 (33 patients)																	
Responsive, 29 patients	17	59	8	28	29	100	2	7	..	..	11	38	11	18	8	21	46
Unresponsive, 4 patients	4	100	4	100	4	100	2	50	..	..	2	50	..	4	3	1	59
Total																	
Responsive, 103 patients	37	36	36	35	78	76	13	13	4	4	32	31	37	66	40	63	48
Unresponsive, 17 patients	9	53	11	65	14	82	9	53	2	12	9	53	3	14	11	6	54

* Consistent with changes ranging from left ventricular hypertrophy to severe myocardial functional derangement.
† Percentages indicate percentage of total responsive or unresponsive patients in each group with each complication.

TABLE 2.—*Incidence of Side-Reactions to Hexamethonium and Hypertensive Symptoms and Signs Relieved or Improved by Its Use*

Side-Reactions Due to Hexamethonium	Duration of Treatment							
	Initial		3 Mo.		6 Mo.		1 Yr.	
	No.	%	No.	%	No.	%	No.	%
Total No. of Patients	120	100	103	100	69	100	34	100
Side-Reaction								
Constipation	92	77	62	60	20	29	8	24
Anorexia	55	46	26	25	13	19	3	9
Weight loss	..	..	32	31	27	39	8	24
Blurred vision	78	65	22	21	8	12	4	12
Fatigue	56	47	38	37	26	38	10	29
Dry mouth	88	73	26	25	10	14	5	15
Nausea and vomiting	31	26	12	12	3	4	1	3
Diarrhea	14	12	8	8	14	20	6	18
Dizziness *	61	51	45	44	31	45	11	32
Impotence †	20	50	25	68	10	45	6	50
Precordial pain	1	1	..	..	..	..	..	..
Abdominal cramps	24	20	12	12	6	9	4	12
Syncope	12	10	6	6	4	6	3	9
Urinary retention	3	3	..	..	..	..	..	..

Symptoms or Signs Improved by Hexamethonium	Total No. of Patients Complaining	Patients Improved	
		No.	%
Symptom or Sign			
Headache ‡	38	30	79
Precordial pain	31 §	22	71
Angina pectoris	15	11	73
Eye ground changes ‖	53	36 ¶	68 ¶
Albuminuria	26	16	62
Hematuria ⁂	22	12	55
Nervous tension	24	18	75
Heart failure	36	26	72
Abnormal ECG strain	48	32	67
Myocardial damage	44	8	18

* Elicited in the upright position at least twice a week.
† Occurred only in males, of whom there were 40 initially, 37 at 3 months, 22 at 6 months, and 12 at 1 year.
‡ Includes headaches following the onset of hypertension not those unrelated to elevated blood pressure.
§ Includes 15 patients with typical angina pectoris.
‖ Includes only those with grade 3+ or 4+ changes according to the Keith-Wagener classification.
¶ Improved to next grade or better.
⁂ Many red cells on microscopic urine examination associated with exacerbation of hypertension. All patients showing improvement of this manifestation had previously had a significant reduction in blood pressure.

* One of the authors (J. H. M.) has had occasion to observe two patients elsewhere treated by a more rapid titration method under hospital conditions, in whom segmental paralytic ileus developed. In one of these, the ileus was relieved within 18 hours after use of the drug was stopped. The second patient was in severe uremia (and had been prior to therapy, also, with a blood urea nitrogen level of 150 mg. per 100 cc.) and had associated lower abdominal pain. The attending physician and a surgical consultant, being aware of this complication, performed a laparotomy, and the patient died within four days from progressive uremia.

the drug was excreted and the blood pressure rose to normotensive or mildly hypertensive levels. When excessive reduction in blood pressure caused concern, any of the peripherally acting vasopressor agents were effective as antidotes for raising the blood pressure, since hexamethonium has no peripheral blocking action. Excessive hypotension and constipation were the most difficult side-effects to handle effectively and still control the hypertension. Cholinergic drugs were of little value for the correction of constipation. Cathartics, in the form of cascara sagrada, liquid petrolatum (mineral oil), and magnesium hydroxide (milk of magnesia), were adequate and were used freely whenever indicated. Intermittent nausea, occasional vomiting, and abdominal cramps were seen frequently, but these were usually observed during the initial period of therapy. Most of the side-reactions decreased as treatment continued. There was one exception. Diarrhea was seen more frequently in patients who had been receiving the drug for prolonged periods. Even after the patients had been on the drug for long periods, if they obtained an increased response to the drug, owing to increased intake, increased absorption, or decreased excretion, the previous symptoms returned as the blood pressure dropped. This was especially true of fatigue, blurred vision, and constipation. Orthostatic dizziness was experienced at some time by the majority of the patients. This suggests excessive reduction in blood pressure. If it occurs at the same time each day, it is an indication for reducing the amount of drug being ingested in the preceding dose. A history of recurrent orthostatic dizziness between clinic visits was of considerable value to the physician in arriving at a correct dose schedule. Owing to some day to day variation in the blood pressure of most patients, an attempt was made to regulate the upright blood pressure at levels slightly above normal (150/90 to 100) to avoid periods of excessive orthostatic hypotension and syncope. Persistent dizziness when standing occurred almost invariably if the supine blood pressure was adjusted to strict normotensive levels. The difference between the supine and upright blood pressure reduction in many patients tended to decrease as therapy was continued, but some orthostatic effect was present even in those who received the drug for a year or more (table 2). Urinary retention occurred in three patients, but in each instance the dosage had been increased rapidly. Hexamethonium therapy was abandoned in two of the three patients, after which this symptom was completely relieved. The retention subsided spontaneously in the third patient, despite continued drug administration. Many of the men experienced some degree of impotence but no alteration in sexual drive. Attempts to occasionally relieve this symptom by omitting the night dose proved ineffective unless the blood pressure also escaped from control. Therefore, in most patients with very severe hypertension, it was thought inadvisable to overcome this complaint or to bring the possibility to the patient's attention. On withdrawal of hexamethonium, the symptom was always relieved.

The most outstanding symptomatic improvements were the relief of headache and angina pectoris. This occurred in three-fourths of the patients with these complaints. Precordial pain associated with the hypertension but not typically anginal in type was also relieved as the blood pressure was reduced. Eyeground examination showed definite objective improvement in numerous instances. This was in the form of reduction of hemorrhages and exudates, which was usually associated with improved vision. Of 53 patients with grades 3+ and 4+ (Keith-Wagener classification) changes due to hypertensive vascular disease, improvement to the next grade or better was noted in 68%. All but two of the patients showing improvement also obtained a significant reduction in blood pressure. In the two exceptions, spontaneous improvement occurred. Although an increase in phenolsulfonphthalein excretion was not observed in most of the patients, progressive impairment also did not

TABLE 3.—*Blood Pressure Response to Orally Administered Hexamethonium*

Follow-up Period *	No. of Patients	Average Dose †		Blood Pressure Response: Upright Control	Upright During Therapy	Upright % of Control	Supine Control	Supine During Therapy	Supine % of Control
Group 1 (29 patients)									
Responsive ‡									
3-6 mo.	7	2538	.....	204/114	141/90	69/79	213/116	171/98	80/84
6-12 mo.	9	3375	.....	200/115	153/99	77/86	203/119	177/103	87/87
1 yr. or more	9	3167	.....	196/114	139/91	71/80	190/107	171/101	90/94
Total	25	....	Mean §	200/114	145/94	73/82	203/115	173/101	85/88
Unresponsive	4	3000	Mean	181/113	161/103	89/91	184/115	182/110	99/96
Group 2 (58 patients)									
Responsive ‡									
3-6 mo.	18	1875	.....	241/129	141/92	59/71	214/130	172/108	80/83
6-12 mo.	13	3500	.....	208/127	153/100	74/79	213/127	174/107	82/84
1 yr. or more	18	2938	.....	198/130	129/84	65/65	205/129	171/107	83/83
Total	49	....	Mean §	216/129	140/91	65/71	210/129	172/107	82/83
Unresponsive	9	4250	Mean	218/131	206/129	94/98	221/123	212/119	96/97
Group 3 (33 patients)									
Responsive ‡									
3-6 mo.	7	3542	.....	223/153	176/125	79/82	228/165	197/134	86/81
6-12 mo.	13	2666	.....	221/147	164/107	74/73	225/145	169/107	75/74
1 yr. or more	9	3125	.....	242/154	148/98	61/64	248/156	179/109	72/70
Total	29	....	Mean §	228/151	164/109	72/72	233/153	179/114	77/75
Unresponsive	4	4250	Mean	230/158	224/152	97/96	233/156	211/154	91/99

* After blood pressure reduction with hexamethonium.
† Milligrams of hexamethonium per 24 hours, given in divided doses.
‡ Mean blood pressure decrease of 20 mm. Hg or more.
§ Mean for total number of patients in group who responded, not an average of the figures in each column.

occur as long as the blood pressure could be controlled. The presence of albumin and red cells in the urine, which was observed during the control studies in many of the more severely hypertensive patients, was diminished. This was especially true in the case of intermittent hematuria that accompanied exacerbations in the hypertension. Of the nine patients with azotemia, three showed a good blood pressure response, but the blood urea nitrogen level increased during maximum hypotensive therapy. This was reversed in one of the three when the blood pressure was allowed to increase to a moderately hypertensive level but one that was still considerably below the control value. Therapy was discontinued in the second. The third patient had malignant hypertension and broke out of control as soon as the dose of hexamethonium was decreased. The blood urea nitrogen level was elevated but returned to normal as the blood pressure responded to treatment but broke out of control, rapidly progressed downhill, and died. Therefore, they are included in the unresponsive group in the present report. Four patients who died never obtained a reduction in blood pressure. Three of these were also given combined hexamethonium and hydralazine (Apresoline) therapy, according to the method of Schroeder, without a response being obtained. The eighth death was due to a cerebral hemorrhage that followed abandonment of therapy on the patient's own volition and against medical advice. None of the patients who obtained and maintained a good reduction in blood pressure with this therapy have died.

Forty-four patients who have been treated with orally administered hexamethonium and who have been followed for one year or more are available for long-term comparison with other patients treated in the same clinic

TABLE 4.—*Comparison of Blood Pressure Response to Hexamethonium with That to Other Hypotensive Drugs Used in the Same Clinic Under Similar Circumstances*

		Percentage of Patients Responding						Follow-Up After 1 Yr.		
	No. of Patients Treated	Normotension*	Decrease in M.B.P.† 40 Mm. or More	Decrease in M.B.P. >30 Mm. but Less Than 40 Mm.	Decrease in M.B.P. >20 Mm. but Less Than 30 Mm.	Decrease in M.B.P., 20 Mm. or More	Daily Dose, Mg.	No. of Patients Followed	Patients Responding‡ No.	Patients Responding‡ %
Dibenzyline §	32	44	47	9	9	66	155	..	..	..
Phentolamine §	24	0	0	8	8	17	675	24	0	0
Anatensol ‖	31	3	3	10	6	19	7.1	31	2	6
Veriloid ‖	30	7	20	7	23	50	18.1	28	6	21
Hydralazine §	52	10	10	8	15	33	641	52	4	8
Hexamethonium § ¶	120									
Group 1	29	31	7	38	38	86	3,013	10	9	70
Group 2	58	38	55	31	..	84	2,938	23	18	78
Group 3	33	20	67	6	13	88	3,169	11	9	82
Mean for all three groups	..	32	47	26	13	86	Total	44	36	82 #

* Maintained below 150 mm. Hg systolic and 100 mm. Hg diastolic (upright).
† M.P.B. = mean blood pressure.
‡ Number of patients who continued to show a decrease in mean blood pressure of 20 mm. Hg or more.
§ Blood pressure response in upright position.
‖ Extract of veratrum viride.
¶ Administered over periods of 3 to 18 months.
# Four discontinued therapy on their own volition after this length of time, and for four others another hypotensive agent (hydralazine) was added to the therapy.

decreased in four patients in the responsive group. Two of the nine patients had malignant hypertension and showed no blood pressure response to the drug. Both have since died as a direct result of their hypertension. The symptoms and signs of heart failure improved as the blood pressure was reduced in about two-thirds of the patients. This occurred in patients who had previously received digitalis and diuretics as well as in the patients who had not received specific therapy for heart failure. Improvement of the cardiac status was verified by observation of a decrease in heart size seen on roentgenograms in numerous instances. In general, the electrocardiograms that showed a left ventricular strain pattern improved; however, when evidence of frank myocardial damage existed, little change was observed. Patients with malignant hypertension and simultaneous cardiac failure and severe renal disease were especially resistant to hypotensive therapy. During the course of this study, eight patients died. Three had malignant hypertension associated with renal disease and heart failure. They originally with other hypotensive drugs. Eight of the 44 failed to obtain a good initial therapeutic response and are included in the unresponsive group. Four others have discontinued use of hexamethonium on their own volition after one year, although they had initially obtained and had continued to have a satisfactory reduction in blood pressure (table 4). In four other patients, hydralazine was added to the therapeutic program, despite an initial and maintained reduction in blood pressure for one year or more when hexamethonium had been used alone. This was done either in an effort to obtain a greater reduction in blood pressure with less side-effects or because the blood pressure seemed excessively labile when hexamethonium was used alone. Therefore, hexamethonium alone has been found to be a satisfactory therapeutic agent for the treatment of hypertension in 64% of the patients who have been treated for one year or more. There is no indication at this time that the drug will not continue to be effective indefinitely in this group of responsive patients.

PHARMACOLOGICAL ACTION

Therapeutic agents that are capable of lowering the blood pressure through their action on the nervous system can be divided essentially into three groups, according to their primary site of action: (1) centrally acting drugs (on the brain), which depress the central outflow of vasoconstrictor impulses (hydralazine and Veratrum viride extracts); (2) ganglionic blocking drugs, which block the transmission of impulses through the autonomic ganglions (hexamethonium); and (3) peripheral blocking agents, which block the transmission of impulses from the sympathetic nervous system to the end organ (phentolamine [Regitine] and Dibenzyline [N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride]). Certain drugs, such as Hydergine (methanesulfonates of dihydrogenated ergotoxine alkaloids), affect more than one focus by acting both centrally and peripherally. Hexamethonium falls into the ganglionic-blocking group of drugs (fig. 1). It, like tetraethylammonium, is exceptional by comparison to other known ganglionic paralyzing agents in that it does not stimulate the ganglions prior to paralysis. It differs from tetraethylammonium in that the paralysis lasts longer and the hypotensive effect is much less variable and more prolonged. Hexamethonium belongs to the bismethonium compounds, which are composed of two ammonium radicals in which the hydrogen ions are replaced by methyl and halogen groups and which are united by a chain of a varying number of methyl groups. The compound so formed is named according to the number of methyl groups in the chain between the two nitrogen atoms. Thus, a compound with 10 methyl groups in the chain is called decamethonium (C_{10}) and one with 6 methyl groups, hexamethonium (C_6). The C_{10} derivatives have been found to have a curare-like action. When hexamethonium produces ganglionic blockade, it blocks the parasympathetic as well as the sympathetic ganglions. Most of the side-effects associated with the reduction in blood pressure can be attributed to the curare-like effect (weakness and fatigue), parasympathetic ganglionic blockade (constipation, urinary retention, dry mouth, and anorexia), or excessive hypotension (dizziness and syncope), which is predominantly orthostatic. Since the drug blocks the cardioaccelerator ganglions to the heart, reflex tachycardia after blood pressure reduction does not occur with hexamethonium as it does following comparable reduction by adrenergic blocking drugs and other means.

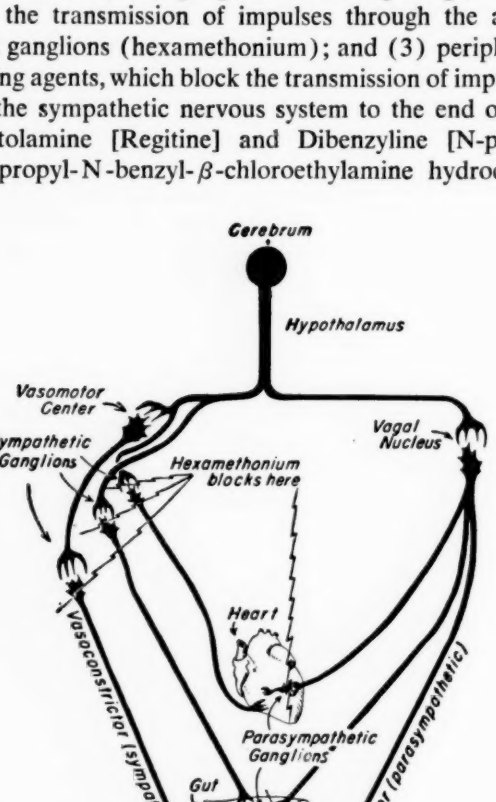

Fig. 1.—Representation of the ganglionic blocking action of hexamethonium. The transmission of vasoconstrictor and cardiac accelerator impulses over the sympathetic nerves to the heart and blood vessels is interrupted following administration of hexamethonium, causing a reduction in blood pressure without a significant change in pulse rate. (Dibenamine is N,N-dibenzyl-β-chloroethylamine).

When blood pressure is reduced, the cerebral vessels dilate and cerebral blood flow and cerebral metabolism are maintained [3a]; however, if the pressure is reduced excessively, cerebral blood flow decreases, and disturbances in cerebral function follow.[3b] This is more likely to occur in the upright position (fig. 2), especially if not accompanied by muscular activity, since reflexes responsible for readjusting vasoconstriction to changes in position are also blocked by hexamethonium. Therefore, the blood pressure should always be measured in both the supine and upright positions in evaluation of ganglionic blocking drug therapy. If cerebral ischemia is to be avoided while the patient is standing, the blood pressure should be adjusted with the patient in the upright position. Note in figure 2 that reduction in blood pressure in the supine position had no significant effect on cerebral blood flow or cerebral oxygen uptake, because of the reduction in cerebrovascular resistance, a result of cerebral arteriolar dilatation. In the upright position, there was a slight reduction in cerebral blood flow. Further reduction in systemic blood pressure was apparently minimized by active motion of the extremities, thus maintaining adequate venous return of blood to the heart. In the 45 degree head-up position with passive tilting there was an additional sharp reduction in systemic blood pressure, and cerebral blood flow was reduced. The patient complained of dizziness just prior to the termination of this aspect of the study. These observations have therapeutic significance with regard to the effect of blood pressure reduction on cerebrovascular hemodynamics. Passive head-up tilt should be undertaken with extreme caution in these patients.

3. (*a*) Crumpton, C. W., and others: Cerebral Circulatory and Metabolic Changes Following Intramuscular Hexamethonium (C-6) Bromide in Subjects with Severe Hypertensive Retinopathy, Federation Proc. **11**: 335, 1952. (*b*) Moyer, J. H.; Miller, S. I., and Snyder, H. B.: Unpublished data.

4. Moyer, J. H., and Mills, L. C.: Hexamethonium—Its Effect on Glomerular Filtration Rate, Maximal Tubular Function (TmPAH) and Renal Excretion of Electrolytes, J. Clin. Investigation **32**: 172, 1953.

5. (*a*) Moyer and Mills.[4] (*b*) Freis, E.: Personal communication to the authors. (*c*) Kelley, R. T.; Freis, E. D., and Higgins, T. F.: Effects of Hexamethonium on Certain Manifestations of Congestive Heart Failure, Circulation **7**: 169, 1953.

Following acute blood pressure reduction with hexamethonium (studies in supine position) there is an initial depression of renal function.[4] Glomerular filtration gradually returns to normal, however, despite a maintained reduction in blood pressure, provided [5] the reduction is not excessive. The patient whose course is shown in figure 3 was admitted to the hospital in a semicomatose state associated with a hypertensive crisis. The blood pressure was reduced acutely with parenterally administered hexamethonium, and renal functions (glomerular filtration rate and renal plasma flow) were depressed as the blood pressure decreased. Despite maintenance of the reduction in blood pressure, renal function returned to normal. The patient was later given the drug orally, and, although blood pressure was maintained at 130 mm. Hg systolic and 100 mm. Hg diastolic, renal function was not depressed in comparison with the pretreatment levels.

Renal blood flow and the glomerular filtration rate are depressed following exercise in untreated patients.

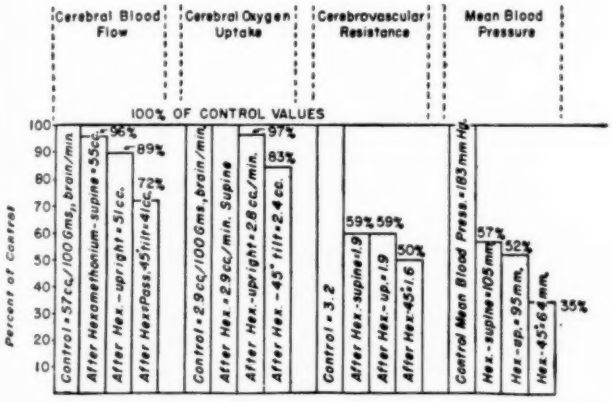

Fig. 2.—Cerebral hemodynamic response to blood pressure reduction with hexamethonium in a patient with malignant hypertension. The effect of reduction in blood pressure in the supine position is contrasted with that in the upright position accompanied by active motion of the legs and that in a 45 degree head-up position with passive tilting.

This also occurs in patients who have been treated with hexamethonium.[6] Patients with renal damage respond to blood pressure reduction qualitatively, similarly to patients with normal kidneys, but the readjustment is slower.[4] A few patients fail to completely readjust [6] to a lowered blood pressure. If readjustment is incomplete, there is little need for concern if renal function is relatively normal; however, if renal function is severely impaired, even small reductions in glomerular filtration may seriously decompensate the excretory capacity of the kidney. Therefore, in the presence of impaired renal function, the therapist must be alert to this possibility. When the blood pressure is reduced excessively, the glomerular filtration rate is depressed, and anuria supervenes, even in the presence of relatively normal kidneys. When this occurs, arterenol infusion will quickly reverse the process, with improvement in glomerular filtration. The patient whose course is shown in figure 4 had a normal glomerular filtration rate during the control period; however, because of excessive reduction in blood pressure with orally administered hexamethonium, glomerular filtration decreased sharply, and anuria supervened. When this patient's blood pressure was increased by means of arterenol infusion, the glomerular filtration rate and urinary output returned toward the control levels. After 12 hours, when arterenol infusion was discontinued, the blood pressure remained elevated, and glomerular filtration approximated the control observations.

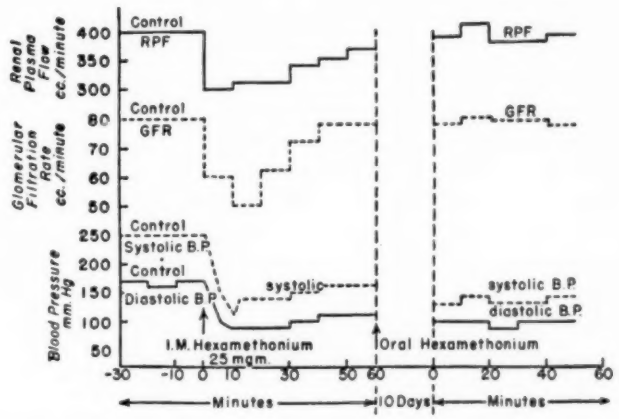

Fig. 3.—Acute response of blood pressure and renal function to intramuscularly administered hexamethonium and their status 10 days later during maintenance therapy with orally administered hexamethonium.

CLINICAL CONSIDERATIONS

The beneficial effects of blood pressure reduction can be argued pro and con. In the hypertensive state there are three vascular beds that are especially likely to cause complications. These are the cerebral vessels, the heart and coronary vessels, and the renal vasculature. The present studies confirm many previous observations that the vascular stress on the heart and cerebral vessels in patients with hypertension is relieved by reducing the blood pressure. Hypertensive headaches were improved in about four out of five patients with this complaint. Relief was obtained without altering cerebral blood flow. As the blood pressure is reduced, the cerebral vessels dilate (fig. 2), and, thus, cerebral blood flow is main-

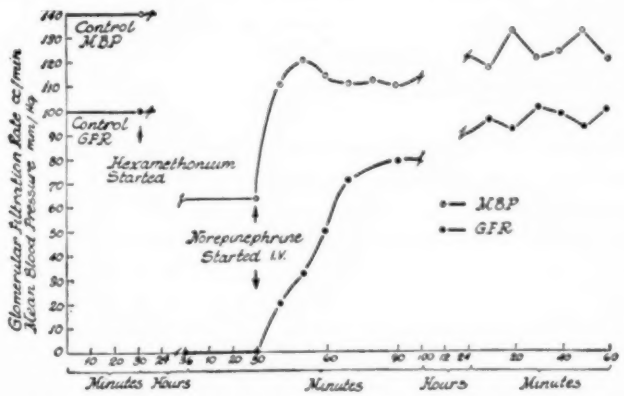

Fig. 4.—Effect of excessive hypotension due to hexamethonium on the glomerular filtration rate in a patient with a normal control rate.

6. Ford, R. V.; Moyer, J. H., and Spurr, C. L.: Hexamethonium in the Chronic Treatment of Hypertension—Its Effect on Renal Hemodynamics and the Renal Excretion of Water and Electrolytes, J. Clin. Investigation, to be published.

tained, even during treatment for severe and malignant hypertension.[3b] If the pressure is reduced excessively, complications, such as cerebral ischemia with thrombosis and paralytic phenomena, may be anticipated. This was not observed, although one older patient experienced transient weakness at a time that her blood pressure had declined to 80 mm. Hg systolic and 50 mm. Hg diastolic in the upright position. As soon as the patient reclined, immediate and complete recovery followed. The manifestations in this instance were probably those of ischemia rather than thrombosis. Apparently, the cerebrovascular dilatation associated with the reduction in blood pressure tends to prevent the formation of thrombi. Certainly, reducing the blood pressure decreases the possibility of occurrence of hemorrhages and small vessel bleeding. This is well demonstrated in the improvement and resolution of retinal hemorrhages in numerous instances as the blood pressure was reduced.

The decrease in precordial pain and improvement of the anginal syndrome in many instances suggests that the ratio of coronary blood flow to oxygen and metabolite demand is improved. In only one instance was coronary pain precipitated by reduction in blood pressure, whereas definite improvement in angina was noted in three-fourths of the patients who had this complication. Improvement was also noted in patients who experienced precordial pain that was not typically anginal in type. Apparently the reduction in work load on the heart compensates for any decrease in coronary flow associated with the drop in arterial blood pressure. It is also possible that ganglionic blockade of either the sympathetic or parasympathetic nerves to the heart inhibits vasoconstrictor impulses traveling to the coronary vessels. In addition, the drug may exert some direct action or it may block afferent sensory nerves traveling over the sympathetics. When the blood pressure was reduced in patients with associated heart failure, cardiac output [5b] increased, and heart failure improved. This observation suggests that the cardiac efficiency is improved as the work load is reduced.

It can be concluded from the above observations that if cerebral pathological changes or cardiac failure exist either alone or in combination and if they are secondary to severe and prolonged hypertension, attempts to reduce the blood pressure should be undertaken. This is particularly true if renal function is not impaired. Contrariwise, if impairment of renal function predominates, caution must be exercised when reducing the blood pressure, since further impairment of renal excretory capacity may occur. Although the damaged kidney responds to a reduction in blood pressure by vasodilatation in a relatively normal fashion, this occurs more slowly [7] than in the normal kidney and is occasionally incomplete. Failure of complete renal hemodynamic readjustment is more likely to occur if the blood pressure is reduced to absolute normotensive or hypotensive levels. In the presence of renal damage, glomerular filtration is critical, and small, absolute changes may throw the patient into frank and progressive renal failure. With normal renal function, the renal reserve is adequate to compensate for minor changes; however, even in this case, if blood pressure reduction is excessive, glomerular filtration is greatly depressed, and anuria supervenes (fig. 4). These observations do not indicate that blood pressure reduction is not feasible in the presence of impaired renal function. They do indicate that, when blood pressure reduction is undertaken, it must be done with extreme caution and with constant evaluation of renal excretory function. Any tendency toward an increase in the blood urea nitrogen level is a definite contraindication to further reduction in blood pressure. When this occurs, the blood pressure must be allowed to return to levels at which renal excretory capacity is not further impaired. Blood pressure reduction with hexamethonium should not be undertaken under circumstances in which determinations of the blood urea nitrogen level are not feasible.

COMPARISON WITH OTHER DRUGS

When hexamethonium is compared with some of the other drugs that currently are being used under similar circumstances, the superiority of the former as a hypotensive agent is obvious (table 4); for example, if semipurified Veratrum viride preparations, such as Veriloid and Anatensol,[8] are administered by the oral route, the blood pressure can be reduced significantly for prolonged periods in only a small number of patients. When enough drug is given to consistently reduce the pressure, nausea and vomiting will be experienced by almost all patients. This limits the usefulness of these compounds, and follow-up after one year indicates that 20% of the patients, or less, continue to obtain any reduction in blood pressure. Only in exceptional patients (3 to 7%) can the blood pressure be reduced to levels approaching normotensive values.

The effectiveness of hydralazine (Apresoline) may be limited when given alone, either orally or parenterally, owing to the tachycardia and increased cardiac output that accompany the reduction in blood pressure.[9] This is a serious consideration in the presence of coronary artery disease, in which myocardial ischemia may develop as a result of the cardiac stimulant effect on a heart in which the coronary arteries are unable to deliver an adequate supply of blood to the myocardium. When the tachycardia is marked, the electrocardiogram shows T wave changes consistent with coronary insufficiency, presumably on the basis of the increased cardiac work.[9b] In studies on the isolated heart-lung preparation, there is some evidence that hydralazine may actually increase the blood flow through the coronary vessels. If this occurs in the intact animal it is apparently not adequate to completely compensate for the increased work load on the heart caused by the tachycardia. When the sympatho-

7. Moyer and Mills.[4] Ford and others.[6]

8. Mills, L. C., and Moyer, J. H.: The Treatment of Hypertension with Orally and Parenterally Administered Purified Extracts of Veratrum Viride and a Comparison with Ganglionic (Hexamethonium) and Adrenergic Blocking Agents, A. M. A. Arch. Int. Med., to be published.

9. (*a*) Freis.[5b] (*b*) Moyer, J. H.; Handley, C. A., and Huggins, R. A.: Some Pharmacodynamic Effects of 1-Hydrazinophthalazine (C-5968) with Particular Reference to Renal Function and Cardiovascular Response, J. Pharmacol. & Exper. Therap. **103**: 368, 1951.

mimetic effect on the heart is previously blocked off by the use of ganglionic blockade (hexamethonium), hydralazine is a valuable adjunct in the treatment of hypertension, since ganglionic blockade does not alter the vasodepressor effect of the hydralazine but blocks at least part of the tachycardia and increased cardiac output [10] that accompany administration of this drug alone. Out of 25 patients who did not obtain adequate hypotensive response to hexamethonium alone, we have been able to reduce the standing blood pressure to normotensive levels in 9 patients, and, in an additional 6, the systolic pressure was reduced more than 40 and the diastolic more than 20 mm. Hg. Schroeder [11] has considered use of combined hexamethonium and hydralazine as the method of choice in the treatment of hypertension. In our opinion, the proper use for hydralazine in the treatment of hypertension is as an adjunct to hexamethonium or to surgical sympathectomy in patients who do not obtain adequate reduction in blood pressure when these procedures are used alone. This conclusion is reached because of the greater difficulty in regulating dosages in combined hexamethonium and hydralazine therapy and the higher incidence of side-reactions, which include headache, diarrhea, dyspnea, nausea, vomiting, and occasional paresthesias.

Phentolamine (Regitine), when given orally in effective doses to patients with essential hypertension, is usually associated with nausea, vomiting, weakness, and headache, so that less than 15% of patients can tolerate the drug for longer than one month. After three months, tolerance develops. Perhaps, the cardiac stimulant effect that has been observed occasionally will be a further contraindication to its widespread use, even by the parenteral route.

Dibenzyline is the most specific and the most effective of the peripherally acting adrenergic blocking agents when taken orally. If the patient would continue taking this drug, hypotension could usually be maintained [12]; however, in patients receiving Dibenzyline reflex tachycardia and palpitations frequently develop as the blood pressure decreases, since the sympathetic nerves to the heart are not blocked. In addition, patients receiving this drug just "feel badly" without being able to identify the complaint, probably a cerebral effect. These side-effects are limiting factors in most instances. The tachycardia is especially difficult to control and is probably a contraindication to the use of this drug in the treatment of hypertension on a long term basis. Tachycardia does not follow the reduction in blood pressure from ganglionic blocking drugs, which block the sympathetic impulses before they reach the heart. Hypotensive reflex tachycardia is not, therefore, a factor in hexamethonium therapy. This is an important reason why long term therapy is so much more successful with hexamethonium than with Dibenzyline.

SUMMARY AND CONCLUSIONS

1. The results obtained with orally administered hexamethonium in treatment of 120 patients with hypertension are summarized. The patients in this study were treated as outpatients and were followed for 3 to 18 months after institution of therapy. The conditions of patient care closely paralleled those met in a general office practice. Therefore, the results obtained in the present study should closely parallel those obtainable in a general office practice, provided the therapist understands the pharmacodynamics of the drug and pays strict attention to the regulation of a dose schedule, which is an individual problem for each patient. There is no set dose, and the drug must be titrated in each patient to establish the proper dose schedule. If this is not done, excessive hypotension and serious complications may result.

2. Hexamethonium chloride, when administered orally, was found to be an effective agent for reducing the blood pressure. Of the 120 patients treated, all but 17 responded with a significant reduction in blood pressure. The amount of drug required was only slightly greater in the patients with diastolic blood pressures above 140 mm. Hg than in those with diastolic pressures less than 120 but more than 100 mm. Hg. No difference could be detected between patients who responded and those who failed to respond, except that patients with severe hypertension complicated by cardiac failure and moderate to severe renal disease seemed to be especially resistant to therapy. After the dose schedules were established, the outstanding problems in therapy were those related to decreased intestinal peristalsis and periodic variability in the hypotensive response. Of the patients treated for one year or more, about 64% are well controlled with hexamethonium as the only therapeutic agent.

10. Moyer, J. H.; Huggins, R. A., and Handley, C. A.: Further Cardiovascular and Renal Hemodynamic Studies Following the Administration of 1-Hydrazinophthalazine and the Effect of Ganglionic Blockade with Hexamethonium on These Responses, J. Pharmacol & Exper. Therap., to be published.

11. Schroeder, H. A.: Control of Hypertension by Hexamethonium and 1-Hydrazinophthalazine: Preliminary Observations, A. M. A. Arch. Int. Med. **89**: 523, 1952.

12. Miller, S. I.; Ford, R. V., and Moyer, J. H.: Dibenzyline: Results of Therapy in Patients with Hypertension and a Comparison with Hexamethonium, 1-Hydrazinophthalazine and Semi-Purified Extracts of Veratrum, New England J. Med. **248**: 576, 1953.

Measurement of Adrenal Cortical Function.—The response of the adrenal cortex to exogenously administered ACTH is one of the most specific and predictable hormonal measurements available. Occasionally, ACTH given intramuscularly is inactivated or destroyed and hence does not reach its target gland—the cortex. Following the intravenous administration of ACTH, this almost never occurs. The response of the circulating eosinophils to ACTH is highly specific as an indication of increased adrenal secretion of 11,17-oxysteroids; this is not true for epinephrine. The measurement of 17-ketosteroid and 11,17-oxysteroid excretion following ACTH administration increases the specificity of the interpretation of the ACTH response and adds an important quantitative evaluation. At present, there is no specific differentiating test for pituitary ACTH deficiency. Progressive increased responsiveness of the adrenal cortex, beginning from a subnormal level, is, however, highly suggestive of either primary, spontaneous pituitary insufficiency or adrenal atrophy secondary to adrenal steroid therapy.—G. W. Thorn, M.D., Measurement of Adrenal Cortical Function, *The Journal of Clinical Endocrinology and Metabolism*, May, 1953.

METHOD FOR THERAPEUTIC EVALUATION OF DIURETIC AGENTS ADMINISTERED ORALLY

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and
Harry Gold, M.D., New York

In the treatment of the patient with congestive failure, the experience of recent years has firmly established the fact that it is the major if not the first order of business to put to work an effective system of diuretic medication. The recognition of this fact has altered the therapeutic approach and results in the management of these patients. In a study published from our clinics a few years ago,[1] it was shown that with the daily mercurial as the nucleus of the regimen for the routine treatment of congestive failure, approximately 90%, instead of the usual 50 to 60%, of hospital patients may be discharged free of congestive failure in an average of about a week, in place of about three or four weeks. One of the points of emphasis in the current planning for this group is that of adequate maintenance with the continued use of potent diuretic agents. The most satisfactory results have thus far been obtained with a maintenance regimen of injections of a mercurial diuretic, some patients being able to carry on satisfactorily with injections at intervals of a week or longer, others requiring two or three injections a week, and some even daily. The problem of frequent injections over a period of years has stirred up interest in the development of new mercurial as well as nonmercurial diuretic agents that might be used by the oral route.

Two of the problems presented by a new orally administered diuretic are similar to those with an injected diuretic, namely, that of diuretic potency and systemic toxicity. The orally administered agent, however, presents a third problem, that of local gastrointestinal irritation and the relation of the intensity of this action to that of systemic toxicity and of diuretic results. This seems to be the chief problem at the present time in regard to the agents currently in use and those experimental materials that we have had an opportunity to examine.

This paper describes results that we have obtained in the endeavor to relate the size of the obstacle of local gastrointestinal irritation to the effectiveness of the diuretic response for several agents that we have recently tested, and calls attention to the kind of orientation that is necessary to understand what can be accomplished and what may be expected of oral diuretic therapy with the materials available at present.

METHOD AND MATERIALS

The diuretic agents shown in the accompanying table were examined for two facts concerning the effects of their oral administration: (1) the diuretic potency and (2) the incidence of sufficient local gastrointestinal irritation to give rise to unpleasant symptoms such as abdominal distress, diarrhea, nausea, and vomiting. The diuretic potency was determined by a method that was recently developed in our clinics [2] for the bioassay of diuretic agents in ambulant patients with congestive failure. The method meets the standard requirements for bioassays and yields results with a high degree of reliability, which is tested by the conventional methods for statistical significance. In essence, the technique is as follows: Selected adult ambulant patients with congestive failure in attendance at the cardiac clinics are accurately weighed, receive an intramuscular injection of meralluride (Mercuhydrin) as the standard, are weighed 24 hours later to ascertain the diuretic effect, and return for another weighing a week later when the loss of weight is usually restored. This is repeated with different doses of the standard. The various doses and the corresponding weight losses are then plotted against each other to form the dosage-response curve. The same procedure is then repeated with the preparation being tested. In the case of the study of cumulative effects from oral medication it is necessary, as in the case of ammonium chloride, to make use of a longer period, treatment for two days or more, between weighings for the diuretic effect. The results are two dosage-response curves from which the relative potency of the standard and the test preparations may be read off directly. In connection with the various doses of the orally administered material utilized for securing the data of the dosage-response curves, records are made of the incidence of disagreeable gastrointestinal effects. Each assay is based on the average response of

Dosage and Effectiveness of Diuretic Agents in Cases of Congestive Failure

Drug	1 Dose, Mg.	2 No. of Patients	3 Effect of the Dose in Terms of Intramuscular Administrations of Meralluride (Cc.)	4 Percentage of Patients in Whom Gastrointestinal Symptoms Developed	5 Rank of Preparations on Basis of Ratio, D. E./T. I.*
Ammonium chloride	16,000	46	0.25	48	52
Meralluride with ascorbic acid	720	25	0.25	32	78
Meralluride †	720	82	0.25	31	81
Theophylline salt †	375	33	0.32	36	89
Aminouracil derivative †	1,000	30	0.36	35	103
Aminophylline	400	33	0.40	30	133
Thiomercurial †	174	44	0.47	25	188
Neohydrin	73.4	38	0.71	25	284

* D. E. = diuretic effectiveness of column 3; T. I. = toxicity incidence of column 4. This is an arbitrary expression showing that one preparation is more favorable than another if it shows a greater diuretic effect for a particular incidence of local toxicity.

† Experimental orally administered preparations not commercially available.

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1. Gold, H., and others: A System for the Routine Treatment of the Failing Heart, Am. J. Med. **3**: 665, 1947.

2. Greiner, T., and others: Bioassay of Diuretic Agents in Patients with Congestive Failure, J. Pharmacol. & Exper. Therap. **103**: 431, 1951.

a group of 25 or more patients, the same patients serving both for the standard and the test preparation as a means of reducing sources of error that would arise from differences between different groups of patients.

RESULTS

In the accompanying table we have assembled the results of such assays with eight diuretic agents—ammonium chloride, several mercurials, an aminouracil, and xanthines. In order to give the data therapeutic meaning, the results are presented in terms of the dose of the agent, the dose of intramuscularly administered meralluride to which its effect corresponded, and the amount of gastrointestinal trouble encountered in a group of patients with a particular dose. To explain the need for this type of analysis, one might take the position that an orally administered diuretic agent would be ideal if it were possible to obtain with each dose in a patient with congestive failure a diuretic response represented by a weight loss of approximately 2 lb. (907.1 gm.), as is the usual case with 1 cc. of meralluride by the intramuscular route, without gastrointestinal side-effects, and that another agent might be considered quite unsatisfactory if, for example, diarrhea developed in two-thirds of the patients with a dose that provided a weight loss of only about 0.5 lb. (226.8 gm.), an effect equivalent to the effect of a 0.25 cc. dose of meralluride intramuscularly. The diuretic effect is expressed in terms of intramuscular meralluride rather than as actual weight loss, since whether the average weight loss for 1 cc. of the mercurial is 1 lb. (453.5 gm.), 2 lb., or 3 lb. (1,360.7 gm.) depends on the amount of edema the particular test group shows. This variation in the weight loss for a particular dose of the diuretic agent does not materially influence the results of an assay for potency by the method that we employ, since the method calls for comparing the test preparations with the standard preparation in the same patients. The data for the preparations included in the table were examined for information relating the diuretic potency to the incidence of gastrointestinal irritation, and an arbitrary expression for the relationship has been utilized to facilitate the ranking of the various materials.

It may be seen that all the orally administered materials produce gastrointestinal distress in some patients. It goes without saying that if the oral doses were small enough the incidence of gastrointestinal symptoms would vanish, but also would the diuretic response. We have therefore selected for inclusion in this table those doses of the various materials that would produce gastrointestinal symptoms in as high as from one-fourth to one-half of the patients, since even here the corresponding doses produced only moderate diuretic effects, and since with lower doses showing less gastrointestinal irritation the diuretic responses become negligible.

The results show that there are marked differences between different diuretic agents given orally when they are examined for their diuretic effectiveness in relation to the corresponding incidence of gastrointestinal irritation. Ranked in terms of the arbitrary expression of this relationship, they showed improvement in practical utility from ammonium chloride with a value of 52 up to one of the most recently developed compounds, Neohydrin (3-chloromercuri-2-methoxy-propylurea),[3] with a value of 284.

This then appears to be the present status of oral diuretic therapy. The range of its utility is a limited one. None is free of unpleasant gastrointestinal side-reactions. It is not possible with any of the orally administered materials to secure such diuretic effects as follow the intramuscular injection of meralluride or similar injectable mercurials in doses of the order of 2 cc. without a prohibitive incidence of gastrointestinal distress. The results show that the average diuretic responses to most of the orally administered materials are in the range that would be represented by about 0.5 cc. of meralluride by the intramuscular route.

COMMENTS

One may consider this situation as favorable or otherwise, depending on the point of view. If one expects from current oral diuretic therapy a substitute for injectable mercurial therapy, the current situation is very unfavorable. On the positive side, there is to be considered the fact that, while for a particular preparation diarrhea may develop in one-fourth or one-half of the patients, there are the patients in the remaining one-half or three-fourths of the group who tolerate it well and may even take larger doses with an adequate diuretic response. These patients are to be discovered only by the method of trial, and when they are found it is in them that the difficult problem of long periods of injections may be eliminated. Another favorable aspect of current oral diuretic therapy is the prospect of substantially prolonging the interval between injections by appropriate dosage with the orally administered materials, especially those with the more favorable ratio between diuretic response and local gastrointestinal irritation. There is need for having other diuretic agents intended for oral use examined in the same way.

In recent editorials,[4] attention was called to the importance of clinical pharmacology in the evaluation of agents intended for therapeutic use. What has been described in this paper is an example of clinical pharmacology that provides the kind of information that should be obtained in connection with all new diuretic agents intended for the oral route before they are put to use in a more general test by the less controlled method of the so-called clinical trial.

3. Greiner, T., and others: Human Assay of 3 New Mercurial Diuretic Agents: A Promising Preparation for Oral Use, Proc. Soc. Exper. Biol. & Med. **80**: 117, 1952. Moyer, J. H.; Handley, C. A., and Wilford, I.: Results over a 2 Year Period on 3 Experimental Diuretics Administered Orally to Patients with Cardiac Failure, Am. Heart J. **44**: 608, 1952.

4. Gold, H.: The Proper Study of Mankind Is Man, editorial, Am. J. Med. **12**: 619, 1952. Beecher, H. K.: Clinical Impression and Clinical Investigation, editoria', J. A. M. A. **151**: 44 (Jan. 3) 1953.

Genes and Mermaids: Causation of Congenital Abnormalities.—Some years ago, there came into my hands for dissection an abnormal fetus of nearly full-term, of the very rare variety known as sympus dipus (with fused legs, showing elements of two fused feet); also called symmelus, or sirenomelus, and more usually a "mermaid." My search for the possible etiology of the condition has led me into many fields of study, from the folk-lore of antiquity down to modern investigations of morphogenesis, as I sought some reasonable explanation for the occurrence of gross abnormalities in general and of this one in particular. This search has so far led me to consider for the "mermaid" (really a "merman") the implications of the modern theory of the gene and its mutations as a possible basis of explanation: hence the title "Genes and Mermaids."—M. F. Hickey, M.D., Genes and Mermaids: Changing Theories of Causation of Congenital Abnormalities, *Medical Journal of Australia*, May 9, 1953.

CLINICAL NOTES

TREATMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA WITH METHOXAMINE

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and
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We wish to call attention to the use of methoxamine hydrochloride (Vasoxyl) [1] in the treatment of paroxysmal supraventricular tachycardia. Not only is this drug effective in arresting the tachycardia, but, because of its powerful pressor action,[2] it is especially useful in cases complicated by vascular collapse, a frequent occurrence.[3] The mechanism of action is believed to be a reflex vagal effect following carotid sinus pressure elevation. Two cases of paroxysmal supraventricular tachycardia complicated by vascular collapse, successfully treated by this agent, have been reported [4] and two more are now added. The first case is one of nodal tachycardia and the second, one of auricular tachycardia.

REPORT OF CASES

CASE 1.—C. M., a 63-year-old man, was admitted to the New Britain General Hospital on July 6, 1952, complaining of tachycardia of sudden onset, accompanied by dyspnea. He had previously experienced two similar attacks of tachycardia; the first occurring two years and the second 10 months prior to admission. These attacks had each lasted about three hours. One was terminated by carotid sinus pressure and the other ended in an unknown manner. Examination revealed a pulse rate of 160 beats per minute, with a regular rhythm. There was no cyanosis or peripheral edema. There were no murmurs or rales in either lung field. The blood pressure was 110/65. An electrocardiogram revealed nodal tachycardia with a rate of 160.

Carotid sinus pressure caused a slight slowing of the pulse rate, but the tachycardia was not stopped. Quinidine therapy was started at 2:30 p. m. of the day of admission, at which time 0.2 gm. was given. This was repeated at hourly intervals for four doses. One-half hour after the last dose, the patient complained of loss of sight and shortly thereafter became delirious and incontinent. Examination revealed the patient to be in a state of vascular collapse, with a blood pressure of 30/10 and a cold, clammy, cyanotic skin.

Methoxamine was given intravenously in a 20 mg. dose. Ten minutes later, the blood pressure was 50/30; the pulse rate was not recorded. Thirty minutes after administration of methoxamine, the pulse rate was 88 and the blood pressure was 80/50. During the next 12 hours, the pulse rate remained at about 85, and the blood pressure rose gradually, stabilizing at 120/90. An electrocardiogram revealed a normal sinus rhythm, with rate of 85. The patient was discharged on the second hospital day.

CASE 2.—M. S., a 65-year-old woman, was admitted to the New Britain General Hospital on Aug. 30, 1952, because of acute glaucoma. A peripheral iridectomy was done at 2:35 p. m. on the day of admission. The patient had a 35 year history of attacks of tachycardia, which were characterized by sudden onset and spontaneous termination. The duration of the attacks was from several minutes to two hours, and they usually occurred several times each year. Results of examination of the heart and lungs were not remarkable.

On the evening of Aug. 31, 1952, the day after the iridectomy, the patient complained of palpitation, substernal pain, and dyspnea. Examination at 10:30 p. m. revealed the patient's skin to be cold and clammy; the blood pressure was 90/85. The apical rate was found to be 200 per minute; the rhythm was regular. There were rales at the bases of both lungs. An electrocardiogram at 10:45 p. m. revealed an auricular tachycardia with a rate of 206. At 11:30 p. m., after carotid sinus pressure and eyeball pressure proved ineffective, 10 mg. of methoxamine was administered intramuscularly. At the next examination at 11:45 p. m., the heart rate was 102 and the blood pressure 120/90. At 12 midnight, an electrocardiogram was taken, which showed a normal sinus rhythm with a rate of 102. The rales at the lung bases decreased gradually, disappearing completely one hour after the injection of methoxamine. There was no further tachycardia during the remainder of the patient's hospital stay.

COMMENT

The rapid and safe action of methoxamine contrasts with the effects of some of the previous methods of treatment. Carotid sinus pressure and other mechanical measures are often ineffective. Orally administered quinidine is slow to act, and intravenous administration of quinidine is attended by some danger. Procaine amide (Pronestyl) hydrochloride, like quinidine, is slow-acting when given by mouth and somewhat dangerous when given parenterally.[5] Because of its myocardial depressant effect, caution is advised when it is used in patients with heart disease.[6] The hazards of methacholine (Mecholyl) are well known, and neostigmine (used in combination with methacholine, because it was ineffective alone) has led to alarming reactions.[7] Lanatoside C given intravenously is generally considered to be superior to quinidine in the treatment of supraventricular tachycardia.[8] This superiority is due to its rapidity and safety. It would appear, however, that lanatoside C is not as rapid in action as methoxamine.

Methoxamine may have an almost immediate effect when given intravenously. In the two cases reported by Nathanson and Miller,[4] the attack was said to have ended within a minute. The order of the rapidity with which methoxamine acts is apparently similar to that of phenylephrine (Neo-synephrine), which admittedly acts more rapidly than lanatoside C,[8] restoring normal rhythm in from 35 to 70 seconds after rapid intravenous injection.[9] Methoxamine is safe because it does not cause cardiac irritability. In this regard it is safer than phenylephrine,[10] which, while terminating supraventricular tachycardia by a mechanism similar to that of methox-

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1. This drug is a synthetic amine, β-(2,5-dimethoxyphenyl) β hydroxyisopropylamine hydrochloride, prepared in the research laboratories of Burroughs Wellcome & Company, Tuckahoe, N. Y. Baltzly, R., and Buck, J. S.: Amines Related to 2,5 Dimethoxyphenyl Amine, J. Am. Chem. Soc. **62**: 164, 1940; Characteristics of β-[2,5-Dimethoxyphenyl]-β-Hydroxyisopropylamine Hydrochloride, ibid. **64**: 3040, 1942.

2. King, B. D , and Dripps, R. D.: The Use of Methoxamine for Maintenance of the Circulation During Spinal Anesthesia, Surg., Gynec. & Obst. **90**: 659, 1950.

3. Wolff, L.: The Cardinal Manifestations of Paroxysmal Tachycardia: Vascular Collapse, New England J. Med. **232**: 527, 1945.

4. Nathanson, M. H., and Miller, H.: Clinical Observations on a New Epinephrine-Like Compound, Methoxamine, Am. J. M. Sc. **223**: 270, 1952.

5. Berry, K.; Garlett, E. L.; Bellet, S., and Gefter, W. I.: Use of Pronestyl in the Treatment of Ectopic Rhythms, Am. J. Med. **11**:431, 1951.

6. McClendon, R. L.; Hansen, W. R., and Kinsman, J. M.: Hemodynamic Changes Following Procaine Amide Administered Intravenously, Am. J. M. Sc. **222**: 375, 1951.

7. Furman, R. H., and Geiger, A. J.: Use of Cholinergic Drugs in Paroxysmal Supraventricular Tachycardia: Serious Untoward Reactions and Fatality from Treatment with Methacholine and Neostigmine, J. A. M. A. **149**: 269, 1952.

8. Barrow, J. G.: Treatment of Paroxysmal Supraventricular Tachycardia with Lanatoside C., Ann. Int. Med. **32**: 116, 1950.

9. Youmans, W. B.; Goodman, M. J., and Gould, J.: Neo-synephrine in Treatment of Paroxysmal Supraventricular Tachycardia, Am. Heart J. **37**: 359, 1949.

10. Nathanson and Miller.[4] Lu, F. C., and Melville, K. I.: Concerning the Effects of Sympathomimetic Agents on Coronary Flow and Heart Action, Recorded Simultaneously, Federation Proc. **10**: 320, 1951.

amine, i. e., reflexly through the carotid sinus and vagus, tends to cause ventricular extrasystoles.[9] Methoxamine is perhaps unique among pressor amines in not causing cardiac irritability. It has been found not to increase the irritability of the cyclopropane-sensitized heart, whereas epinephrine, arterenol, and numerous other pressor amines commonly produce either supraventricular or ventricular tachycardia.[11] Clinical tests by Nathanson and Miller [4] provided further evidence that methoxamine does not cause cardiac irritability. They found that, when it was administered to six patients with heart block, it did not cause an increase in the ventricular rate. In contrast, epinephrine and to a lesser degree arterenol do cause an increase in ventricular rate in heart block.[12] They found also that methoxamine did not inhibit the production of cardiac standstill by carotid sinus pressure in six patients with sensitive carotid sinuses. In contrast, epinephrine consistently abolishes the ability of the sensitive carotid sinus to produce cardiac standstill. They also found that production of a tendency toward bradycardia is the characteristic effect of methoxamine on normal sinus rhythm.

SUMMARY AND CONCLUSIONS

Methoxamine, a powerful pressor drug, successfully ended attacks of supraventricular tachycardia complicated by vascular collapse in two patients. This drug is characterized by great rapidity of action, and it differs from many other pressor amines in that it does not cause cardiac irritability. If further experience confirms its safety, it may prove to be the drug of choice in the treatment of supraventricular tachycardia.

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SUBACUTE THYROIDITIS TREATED WITH CORTISONE

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The clinical entity known variously as subacute nonsuppurative thyroiditis, deQuervain's disease,[1] or pseudotuberculous thyroiditis is characterized by a tender, firm, inflammatory enlargement of the thyroid gland resulting in (1) fever, (2) pain at the site of involvement and referred to either or both ears, (3) pain or difficulty in swallowing, (4) cough due to tracheal irritation, (5) a mildly hypermetabolic state, (6) marked elevation of the erythrocyte sedimentation rate, and (7) leukocytosis with polymorphonucleosis. This syndrome is readily recognizable and is entirely distinct, both clinically and pathologically, from other nonsuppurative thyroid conditions such as Riedel's struma and Hashimoto's disease.[2]

The cause of this inflammatory disease of the thyroid gland is not known, but it may be of viral origin. The pathological picture is that of intense inflammation with marked polymorphonuclear infiltration of the colloid follicles, forming what appear to be tiny miliary abscesses or pseudotubercles. These have been so named because they appear as circularly arranged groups of foreign body giant cells. The disease may be mild and self-limited, responding adequately to bed rest and administration of iodides, or it may be severe, excruciatingly painful, and may result in persistent fever and disability. The excellent response to cortisone of a patient with subacute nonsuppurative thyroiditis is the subject of this report.

REPORT OF A CASE

A 33-year-old woman was admitted to the hospital on Aug. 12, 1952, with complaints of weakness, malaise, and pain in the left side of the neck for a period of one month. A low grade, variable fever had been observed during that time. Pain in the neck radiated to the head and to the inside of the left ear. The illness had not been preceded by any known upper respiratory infection, and the patient's history was noncontributory. The signficant physical observations were obesity, temperature of 100.6 F, and moderate enlargement of the left lobe of the thyroid gland, which was firm and markedly tender. No enlarged cervical lymph nodes were palpated, and no signs of hyperthyroidism were observed. A diagnosis of subacute nonsuppurative thyroiditis was made. Laboratory studies showed an erythrocyte sedimentation rate of 82 mm. in one hour, basal metabolic rate of -9%, hemoglobin level of 77% (12.3 gm. [Sahli]), 4,010,000 erythrocytes, and 16,500 leukocytes, with 64% polymorphonuclears, 10% stab cells, 25% lymphocytes, and 1% monocytes. Serologic tests were negative, and blood sugar and blood urea nitrogen levels were within normal limits. No deviation of the esophagus was noted in barium studies.

Treatment consisted of bed rest, strong iodine (Lugol's) solution, 7 drops three times daily, aureomycin hydrochloride, 250 mg. four times daily, and analgesic agents for relief of pain. Rectal temperature remained about 100 F, but the patient felt somewhat better and asked to be discharged after five days of hospitalization. There was little change in the tenderness or size of the left lobe of the thyroid. One week later all medication was discontinued, and the patient returned to work. After three days the pain became severe. Both sides of the neck became extremely tender and painful, with pain radiating into both ears and to both sides of the head. Severe pain on swallowing was noted for the first time. The temperature rose to 102 F. The patient was readmitted to the hospital in acute distress. The entire thyroid gland, including the isthmus and pyramidal lobe, was markedly enlarged. Laboratory studies showed an erythrocyte sedimentation rate of 126 mm. in one hour, a hemoglobin level of 70% (11.2 gm.), 3,920,000 erythrocytes, and 19,000 leukocytes, with 74% polymorphonuclear neutrophils, 6% stab cells, 18% lymphocytes, 1% monocytes, and 1% eosinophils.

Treatment again consisted of Lugol's solution, 7 drops three times daily, and aureomycin, 250 mg. four times daily. Frequent injections of meperidine (Demerol) hydrochloride and oral administration of codeine were necessary, but even these did not control the pain and discomfort. After two days, cortisone acetate, in four divided doses totaling 100 mg. daily was given by injection, and the patient was placed on a low-sodium diet (less than 500 mg. of salt daily). Diminution in pain and tenderness was observed after the first two injections of cortisone. Within 36 hours, virtually all tenderness had disappeared from the thyroid gland, and 24 hours later, the pain was entirely gone. A distinct decrease in the size of the gland was noted 48 hours after cortisone therapy was begun, and further rapid decrease was noted during the next five days. The temperature remained elevated for four days and thereafter returned to normal levels. Four days after institution of cortisone therapy the leukocyte count fell to 14,500 and one week later had

11. Stutzman, J. W.; Pettinga, F. L., and Fruggiero, E. J.: Cardiac Effects of Methoxamine (β [2,5-Dimethoxyphenyl]-β Hydroxyisopropyl Amine HCl) and Desoxyephedrine During Cyclopropane Anesthesia, J. Pharmacol. & Exper. Therap. **97**: 385, 1949.

12. Nathanson, M. H., and Miller, H.: The Action of Nor-Epinephrine and of Epinephrine on the Ventricular Rate of Heart Block, Am. Heart J. **40**: 374, 1950.

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2. (*a*) Crile, G., Jr.: Thyroiditis, Ann. Surg. **127**: 640, 1948. (*b*) Lasser, R. P., and Grayzel, D. M.: Subacute Thyroiditis, Struma Fibrosa, Struma Lymphomatosa: A Clinical-Pathological Study, Am. J. M. Sc. **217**: 518, 1949.

fallen to 12,500. The sedimentation rate remained high and declined slowly, so that after 12 days of cortisone therapy it was still 105 mm. in one hour. After eight days of cortisone therapy, 100 mg. per day, the dose was reduced to 50 mg. daily in four divided doses. The pyramidal lobe again became tender and slightly enlarged. The dose was increased to 75 mg. daily, and the symptoms subsided. The patient was then discharged from the hospital and maintained on orally administered cortisone, 75 mg. daily in four divided doses. After another week (19 days of therapy), the sedimentation rate had fallen to 18 mm. in one hour. Cortisone therapy, 50 mg. daily, was continued for another week and then discontinued entirely. No further recrudescence of the thyroiditis was observed, and there was no return of pain, tenderness, or fever. When seen one month later, the patient had remained entirely well. The basal metabolic rate obtained at that time was −15%. There was still some residual enlargement of all lobes of the thyroid gland. Neither hyperthyroidism nor myxedema has so far been observed.

COMMENT

Cortisone may be expected to influence subacute nonsuppurative thyroiditis favorably because of its action of suppressing inflammatory reactions, regardless of their cause. Cortisone provides a means of rapidly bringing the severe pain under control and of arresting the progress of this disease that presumably results from the presence of a marked inflammatory change in the thyroid gland and local structures. Cortisone may exercise a second therapeutic effect by depressing thyroidal activity, and it has been observed to depress the uptake of radioactive iodine [3] by the thyroid gland. This seems to indicate that cortisone effects a reduction in hormone production and colloid formation. The use of cortisone in thyroiditis has already been reported by Crile,[4] who noted a rapid reduction in the size of the gland and decrease in pain and tenderness. He stated, however, that recrudescence followed withdrawal of cortisone after short courses of therapy. It is possible that there was no recurrence in the case reported here because cortisone therapy was continued until after the sedimentation rate had returned to normal levels. This process did not occur rapidly, but required about three weeks' time. The return of the sedimentation rate to normal levels might be used as guide to cessation of cortisone therapy.

Other therapeutic measures, such as administration of Lugol's solution, penicillin, or other antibiotics, have not been conclusively shown to affect the course of this disease and did not do so in the present case. Radioactive iodine administration would not have been effective, because there is very little uptake by the gland during the inflammatory, acute phase of thyroiditis.[5] Radiation therapy (600 to 700 r) has proved very useful but generally requires one to two weeks to reach full effect.[6]

A case has recently been reported in which thyroiditis developed while the patient was receiving cortisone therapy for rheumatoid arthritis.[7] However, in view of the fact that the thyroidal swelling became fluctuant and that the radioiodine uptake by the gland was 35%, it is probable that the condition was of a true suppurative or bacterial nature. The pathological process would then be entirely different from that of the case reported here.

3. Perry, W. F.: The Action of Cortisone and ACTH on Thyroid Function, Endocrinology **49**: 284, 1951. Freedberg, A. S.; Chamovitz, D. L., and Kurland, G. S.: Thyroid Function in Normal and Pathological States as Revealed by Radioactive Iodine Studies: II. Factors Influencing the Uptake and Turnover of I^{131} by the Thyroid Gland, Metabolism **1**: 36, 1952.

4. Crile, G., Jr.: Thyroiditis, Ann. Int. Med. **37**: 519, 1952.

5. (*a*) Hamilton, H. E.; Kirkendall, W. M., and Barker, S. B.: Radioactive Iodine Uptake of the Thyroid and Plasma Protein Bound Iodine in Subacute Thyroiditis, J. Clin. Investigation **29**: 819, 1950. (*b*) Crile, G., Jr., and Rumsey, E. W.: Subacute Thyroiditis, J. A. M. A. **142**: 458 (Feb. 18) 1950.

6. Crile.[5a] Crile and Rumsey.[5b]

7. Traut, E. F.: Thyroiditis During Treatment with Cortisone, J. A. M. A. **149**: 832 (June 28) 1952.

SUMMARY

A patient with severe, febrile, painful, nonsuppurative subacute thyroiditis showed rapid remission of the symptoms and signs of the disease when treated with cortisone. Recrudescence did not occur when therapy was continued until after the sedimentation rate had returned to normal levels. Other therapeutic measures such as administration of strong iodine (Lugol's) solution, penicillin, and aureomycin did not appear to affect the course of the disease.

177 New York Ave.

POISONING IN A CHILD SIMULATING DIABETIC COMA

REPORT OF A CASE

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The clinical and laboratory picture resulting from the ingestion of poisons is often varied and bizarre. We have found no report in the literature, however, of a condition simulating diabetic coma that followed the swallowing of poisonous berries.

REPORT OF CASE

A 5-year-old white girl was admitted to the Beth El Hospital on Aug. 26, 1952, with the chief complaints of vomiting, abdominal pain, and fever. The child was apparently well until the night before admission, when she complained of pain in the abdomen and vomited. The temperature was normal. The next morning the pain became more intense and localized mostly about the umbilical region. The vomiting continued, and the vomitus was bile stained; the temperature rose to 102 F. A blood count and results of a urinalysis were found to be within normal limits. In the next few hours the child's general condition grew worse, and she was hospitalized.

The past history disclosed nothing remarkable. She had not suffered from any childhood diseases; a maternal grandfather had diabetes. The parents were questioned closely as to the possibility of the child having swallowed some poison, but they denied knowledge of any such act.

On admission, the picture presented was that of an acutely ill child who was semicomatose and had a temperature of 105 F. The pulse was rapid but regular, and the respirations were not labored. The skin was hot, dry, and free of any discoloration. The pupils were somewhat dilated but reacted to light. There was no neck rigidity; no abnormal reflexes were elicited. The heart and lungs were normal. There was some spasm and rigidity of the recti muscles, but no abdominal tenderness. A 5% solution of glucose in sodium chloride solution was given intravenously, but before this was done blood was drawn for chemical studies, and the child was catheterized for a urine specimen. The subsequent findings were revealing. The urine specimen was free of albumin but showed 4+ glucosuria and acetonuria. The blood chemical findings disclosed a glucose

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Mr. Landon Winchester, Botanist of the Brooklyn Botanical Gardens, identified the plant that had poisoned the child.

content of 290 mg. per 100 cc. and a carbon dioxide combining power of 14 vol. %.

After we received this report, our impression was that we were dealing with some overwhelming infection and diabetic coma. In view of the report that the urine was normal prior to hospitalization, it was decided to withhold insulin therapy until further laboratory study. Intravenous administration of fluid in the form of 1/6 molar lactate and distilled water instead of glucose solution was begun. Antibiotic therapy was given, consisting of one million units of penicillin intramuscularly every three hours and 100 mg. of oxytetracycline (Terramycin) in 50 cc. of distilled water intravenously every four hours. Adrenal cortical extract was administered, with 10 cc. given initially and 5 cc. every four hours.

At 8:20 that evening the temperature rose to 106 F, and the child began to have tonic and clonic convulsions. Phenobarbital was given intramuscularly to control the seizures. At 9:20 p. m. the blood glucose level fell to 210 mg. per 100 cc., without insulin therapy; there was 3+ glucosuria, but the twitchings and seizures still persisted and the temperature remained high. A spinal tap done at this time revealed normal fluid content. After continuous antipyretic and hydrotherapy, the temperature fell to 103 F at midnight and the glucosuria was 2+. The convulsions were diminishing. At 6 a. m. the child called for its mother and began taking fluids by mouth. At 10 a. m. the temperature was 100.2 F, and the child sat up. The following day, 48 hours after admission the child was afebrile, and all the laboratory findings were within normal limits. The child was discharged on the fifth day of hospitalization.

One week after the child was discharged, we were notified by the mother that the child confessed to having eaten some berries picked off a bush in the park, just prior to the onset of the illness. A twig with some of the berries was submitted to the Brooklyn Botanical Garden for identification and was subsequently shown to be Rhodotytos of the rosacea family, a bush imported from Japan whose berries are called "jet beads."

These berries contain the glycoside amygdalin, which, when ingested, breaks down into hydrocyanic acid. Dr. John C. Krantz, professor of physiology of the University of Maryland Medical School, advanced a possible explanation of the clinical condition found in our case. He stated that "it was possible that this drug (hydrocyanic acid) has a centric action in the region of the hypothalamus and that as one has here a glycemic center as well as a heat center, each of these may have been effected by the drug, producing a hyperthermia and simultaneously contributing to the hyperglycemia."

COMMENT

It is difficult to estimate the actual number of accidental poisonings that occur in children, because as a rule only unusual or fatal cases are reported. Aikman [1] considers that the fatal cases alone amount to about 800 a year in the United States. Where the clinical picture is irregular and confusing and poisoning is suspected, the parents and other persons in close contact with the patient must be questioned closely. Although we did not elicit such a history, our clue that this might not be a true diabetic coma was suggested by the report of normal urine obtained several hours prior to admission. A public health question is also posed by this incident because of the evident availability to children of poisonous berries in city parks.

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1. Aikman, J., in Brenneman's Practice in Pediatrics, McQuarrie, I., editor, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 1, chap. 17, p. 3.

COUNCIL ON PHARMACY AND CHEMISTRY

REPORT TO THE COUNCIL

The Council has authorized publication of the following report from its Committee on Research.

R. T. STORMONT, M.D., *Secretary.*

The Committee on Research, through its Subcommittee on Steroids and Cancer, is sponsoring a collaborative study on steroids and mammary cancer. Reports summarizing this work have been published (Estrogens and Androgens in Mammary Cancer: A Progress Report, report of the Council on Pharmacy and Chemistry, J. A. M. A. **140:***1214 [Aug. 13] 1949. Proceedings of the First Conference on Steroid Hormones and Mammary Cancer, American Medical Association, Chicago, April 4-7, 1949. Current Status of Hormone Therapy of Advanced Mammary Cancer, report of the Council on Pharmacy and Chemistry,* J. A. M. A. **146:***471 [June 2] 1951). In the following report, the conclusions expressed are those of the authors, and final conclusions of the Subcommittee must await evaluation of the studies now in progress.*

PAUL L. WERMER, M.D., *Secretary.*

EFFECTS OF INTENSIVE SEX STEROID HORMONE THERAPY IN ADVANCED BREAST CANCER

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Intensive therapy with estrogens and androgens is employed in the palliative treatment of advanced cancer of the breast.[1] Since observations of the systemic effects and complications of this therapy may provide a clue to the mode of action of the sex steroids in breast cancer, they may be important. Many effects of sex hormone therapy have been recorded, but additional manifestations not commonly recognized have become prominent and more frequently noted at the higher dosages usually employed in breast cancer. The purpose of this report is to record these reactions and their relative frequency with intensive and prolonged hormone therapy.

The duration of treatment varied from a few days to several years. Deleterious reactions occurred early in some patients, necessitating discontinuance of therapy. Thus, effects that might have occurred at later intervals could not be recorded. Most of the patients, however, were treated for a minimum of one month, and a large majority received continuous therapy for considerably longer periods. The causes of the shorter periods of observations were as follows: (1) development of later re-

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The following pharmaceutical firms supplied the hormones used in this study: Ayerst, McKenna & Harrison Limited, conjugated estrogenic substances (Premarin); Ciba Pharmaceutical Products Incorporated, testosterone propionate (Perandren) and ethinyl estradiol (Eticylol); Schering Corporation, testosterone propionate (Oreton) and ethinyl estradiol (Estinyl); E. R. Squibb & Sons, diethylstilbestrol and dienestrol; Wallace & Tiernan Products, Inc., mestilbol (Monomestrol) and dimethyl ether of diethylstilbestrol; and White Laboratories, Inc., dienestrol.

actions necessitating cessation of therapy; (2) discontinuance of use of the hormone because of rapidly progressing disease; (3) systematic interruption, a procedure in the therapy program, whenever an excellent response was obtained;[1k] or (4) death of the patient.

It will be shown that the incidence and degree of effects continued to increase as therapy was prolonged. Since some of the effects were not recognized at the beginning of the study, the data presented represent the absolute minimum but reflect the potentialities of long-term therapy.

TABLE 1.—*Minimal Incidence of Side-Effects of Testosterone Propionate in Eighty-Two Patients with Advanced Breast Carcinoma*

Side-Effects	No. of Cases Analyzed *	No. Demonstrating Side-Effects	Incidence, %
Hoarseness	77	47	61
Hirsutism	75	40	52
Hair loss	55	12	22
Acne	71	21	30
Ruddy complexion	64	28	44
Drowsiness	70	7	10
Nausea	71	13	18
Vomiting	70	8	11
Feeling of well-being	76	58	76
Weight increase	76	54	71
Libido increase	59	22	37
Edema	67	11	16
Hypercalcemia	73	7	10
Uremia	72	3	4

* Figures in this column represent those patients in whom positive or negative observations were recorded.

SPECIFIC EFFECTS OF ANDROGENS

These data are based on an analysis of 82 consecutive female patients with advanced breast cancer who received 50 to 100 mg. of testosterone propionate in oil, intramuscularly, three times weekly (table 1).

Hoarseness.—Hoarseness, which was the commonest of the masculinizing phenomena resulting from androgen therapy, occurred in a minimum of 61% of the patients. The incidence increased with prolonged or more intensive therapy (fig. 1). The changes varied from slight huskiness to a coarse, deep, masculine voice. Some patients complained of a persistent cold, sore throat, or rasping voice; others experienced constriction of the larynx and easy fatigability (or "cracking") of the voice. Singers found they could utter only discordant sounds. Apparently, these laryngeal changes are similar to those that develop in boys at puberty. Androgenic hormones produce hypertrophy of the vocal cords and, if continued, may lead to enlargement of the larynx.[2] Laryngoscopic examination of women in whom these changes develop reveals a generalized, suffused swelling, with injected blood vessels running the length of the cord. A pale, off-white color is a consistent feature of the late changes.[3] Edema occurs first, but hypertrophy of the muscle of the cord may result later. In the majority of our patients, discontinuation of the male hormone was usually followed by a gradual return of an essentially normal voice. In others, the voice failed to return to pretreatment quality, which undoubtedly resulted from persistence of the hypertrophy of the vocal cords.

Hirsutism.—Hirsutism occurred in at least 52% of patients and was generally more noticeable in brunettes and in women with a tendency to hirsutism. The degree of hirsutism varied. With intensive and prolonged treatment, hirsutism usually increased and simulated a more typical masculine distribution (fig. 1). Extreme hypertrichosis, characteristic of masculinizing tumors, was also observed. Variants in the sites of hair distribution were commonly seen. This raises the question of the receptor capacities of the end-organ. The presence of increased hair, especially on the face, disturbed many women and prompted measures for its removal. This induced-hypertrichosis, as a rule, gradually disappeared after cessation of therapy.

Alopecia.—Partial loss of scalp hair, often associated with hypertrichosis elsewhere, was noted in 22% of the patients. The hair of the scalp became dry and coarse and fell out whenever it was combed. Recession at the temples was noted in some patients, and occasionally baldness of the vertex of the scalp resulted. When use of the hormone was stopped, hair reappeared in these areas. Although hair loss occurs in other debilitating diseases, these women generally felt well and maintained satisfactory nutritional states. Occasionally, the hair of patients who received large doses of androgens turned gray. It has been postulated that androgens produce alopecia primarily in persons who have a hereditary susceptibility to baldness. This was strikingly demonstrated in eunuchoids who received androgen therapy.[4] Queries of women in whom such changes developed revealed that their male predecessors had had a high incidence of spontaneous alopecia.

Dermatological Changes.—Aesthetically distressing was the appearance of acne. The lesions resembled those seen in puberal children and varied from small milia and scattered papules to extensive furuncles and papules over the face, back, and chest. Increased oiliness and thickening of the skin also were noted. Known effects of androgens have been suggested to explain the acne: an increase in sebaceous secretion and hyperplasia of the epithelial cells at the mouth of the hair follicle.[5] With superimposed infection, papules and pustule formation may follow. The customary measures for skin hygiene were of benefit in the treatment of the acne, although cessation of therapy was usually followed by remission of this complication. In addition, women with brittle nails noted softening, increased flexibility, and a decrease in chipping. These effects were previously unobserved after prolonged androgen therapy but were confirmed on examination.

Ruddy Complexion.—The complexion of patients treated over long periods frequently became ruddy and flushed, sometimes resembling the faces of patients with Cushing's disease. The face, anterior neck, chest, and occasionally the extremities became erythematous and blanched when pressed. The skin was usually warmer than normal, and patients complained of constant hot flushing unlike that of the menopause. Women who ordinarily had cold hands and feet were often relieved of this condition.

In a substantial number of patients with ruddiness of complexion, hemoglobin values rose from subnormal or normal levels to those as high as 19 gm. per 100 cc. An elevation of the red blood cell count to 6 million cells and an increase in the hematocrit values accompanied the rise in hemoglobin. The mechanism of this hemopoietic stimulation by androgens is unexplained, but bone marrow studies of 12 patients revealed hyperplasia of the erythroid elements. The apparent increase in red blood cell volume or a vasomotor response may account for the flushing. Both ruddiness and flushing disappeared rapidly after omission of testosterone, but the hemoglobin level remained elevated for weeks.

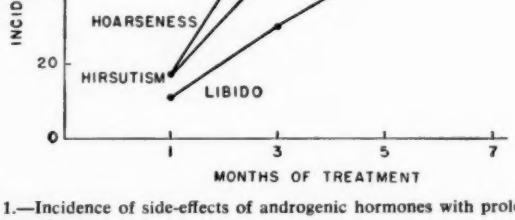

Fig. 1.—Incidence of side-effects of androgenic hormones with prolonged, continuous therapy.

Increased Weight and Well-Being.—One of the most consistent effects observed was a feeling of well-being, which was recorded in 76% of the cases. Patients depressed and debilitated by the disease often became euphoric. Well-being appeared to be an effect of the androgen itself, irrespective of the course of the disease. This symptomatic response was very noticeable in some patients, despite progress of the cancer. Patients frequently bedridden by pain and debility, particularly from osseous lesions, became rehabilitated. X-ray examination of these patients sometimes revealed actual progression of osteolytic lesions. This discrepancy between the subjective and objective responses, which occurred to a lesser degree in a fairly large percentage of patients, emphasizes the difficulties encountered in evaluating the response of the tumor when based on symptomatology alone.[6] Occasionally relief of pain as a result of testosterone therapy was more satisfactory than that obtained from morphine, which suggested an analgesic action.[7]

TABLE 2.—*Incidence of Side-Effects of Estrogens Observed in 235 Patients with Advanced Mammary Carcinoma*

Side-Effects	No. of Cases Analyzed *	No. Demonstrating Side-Effects	Incidence, %
Anorexia	228	129	57
Nausea	230	133	58
Vomiting	223	72	32
Abdominal distress	209	12	6
Diarrhea	201	10	5
Dizziness	189	8	4
Headache	189	13	7
Drowsiness	189	16	8
Libido increase	141	3	2
Nipple pigmentation	188	150	80
Areolar pigmentation	185	143	77
Axillary pigmentation	114	46	40
Scar pigmentation	68	12	18
Skin rash	142	2	1
Itching	143	6	4
Breast engorgement	178	36	20
Breast tenderness	179	29	16
Vaginal bleeding	186	63	33
Withdrawal bleeding	121	51	42
Amenorrhea	8	7	88
Urinary urgency and incontinence	149	41	28
Edema	193	65	34
Congestive failure	191	17	9
Congestive failure (deaths)	191	5	3
Hypercalcemia	...	2	..

* Figures in this column represent those patients in whom positive or negative observations were recorded.

Some patients gained so much weight that they became obese, dyspneic, and generally uncomfortable. At times, it was necessary to give these women a reducing diet during active androgen therapy. These effects can be partially explained by the anabolic capacities of the androgens, which may produce nitrogen retention and promote protein synthesis, with a resultant gain in body weight and increase in muscle tone. Fluid retention in some patients, which may be an accompaniment of androgen therapy without evidence of edema, can account for small weight gains as explained later.

Increased Libido.—After some months of androgen therapy, 37% of the patients noted an increase in libido; the incidence increased with prolonged therapy (fig. 1). This may not represent the true incidence, since some patients were reluctant to discuss it even during direct questioning. The sensation was expressed as a heavy feeling in the pelvis, an increase in the frequency of the sexual act, or a loss of previous frigidity. The degree of accentuation of these sexual impulses varied. Married women were emotionally less disturbed than widows or spinsters. Some found the change so unpleasant that use of the hormone was discontinued. A relatively prompt disappearance of the symptoms usually followed within a short time. This is in accord with previous studies, indicating that androgens cause an increased susceptibility to psychosexual stimulation, enlargement of the clitoris, increased sensitivity of the external genitalia, and a greater intensity of sexual gratification.[8] The clitoris of each patient was not examined systematically, but cursory observations revealed definite enlargement in a number of patients during androgen therapy. An incidence of 28% was reported.[9] The increased feeling of well-being and improvement of the breast cancer might possibly have contributed to this libido-inciting effect.

Drowsiness, Nausea, and Vomiting.—A few patients noted headaches, drowsiness, nausea, and vomiting of brief duration at the beginning of androgen therapy, apparently unassociated with hypercalcemia. Serum calcium determinations were normal. These effects seemed to be produced by other reactions of the hormone, although the presence of incipient or transient hypercalcemia must be considered when they occur. In no patient were these symptoms severe enough to necessitate discontinuance of therapy.

SPECIFIC EFFECTS OF ESTROGENS

Data were available for analysis of the effects of estrogens in 235 cases (table 2). Diethylstilbestrol was used as the reference standard in 178 patients. The usual dosage was 15 mg. per day orally, but variations from 5 to 400 mg. daily were used. Equivalent dosages of other natural and synthetic estrogenic hormones were employed. All but 20 patients included in the analysis received continuous treatment for at least one month and several for more than one year. The remaining patients discontinued the medication early because of severe anorexia, nausea, and vomiting.

Gastrointestinal Symptoms.—Anorexia, nausea, and vomiting, the commonest gastrointestinal symptoms, were fleeting at the start of therapy but persisted in some patients. Of 235 patients, 58% had variable degrees of nausea, and vomiting occurred in 32%. With careful attention to the management of these symptoms and adjustment of dosage, the patient usually became tolerant to more intensive and prolonged therapy. If the patient became severely nauseated by the initial dosage, the daily dose of the hormone was decreased or administered only at bedtime. Gradually the dose was increased as tolerated, until the desired dosage could be administered. Occasionally, despite all efforts, patients were unable to accept the standard dose of the initial estrogen but could tolerate smaller amounts or another estrogenic preparation. This latter phenomenon needs clarification. A small percentage of patients were unable to tolerate estrogenic hormones of any kind at any dosage. The incidence and degree of gastrointestinal symptoms decreased with advancing years (fig. 2). The usual measures to combat nausea and vomiting have seldom been of value in the management of patients treated with estrogen. Patients who tolerated an initial course of estrogens sometimes experienced nausea and vomiting during interrupted courses of the hormone or, occasionally, later during continu-

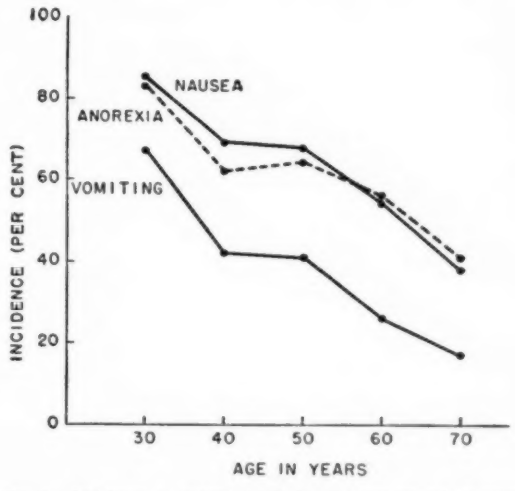

Fig. 2.—Incidence of gastrointestinal symptoms caused by estrogens, with respect to increasing age.

ous treatment. In a few patients, epigastric pains of short duration were noted. In others, soft or increased frequency of bowel movements or diarrhea occurred, but rarely were these symptoms severe enough to warrant treatment or discontinuance of the hormone.

Dermatological Changes.—In elderly women with dry, coarse, atrophic skin, occasionally increased tissue turgor and softening of the skin developed after prolonged estrogen

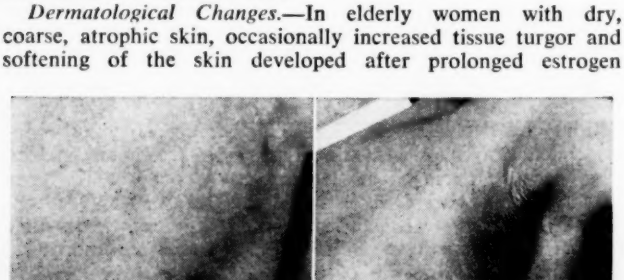

Fig. 3.—Appearance of areola, nipple, and axilla: *A*, prior to estrogen therapy, and *B*, after four months of estrogen therapy. Note the stippled appearance of the pigmentation in linear folds of the axilla.

therapy. A few patients noted flushing of the face, which was seen frequently after administration of testosterone. Itching occurred in a few persons. Rarely, skin lesions consisting of diffuse areas of small papules or erythema were noted.

Pigmentation.—Pigmentation of the nipples was present in about 80% of the women treated with estrogenic hormones. The earliest and sometimes the only change was a redness of the nipple and areola, particularly in patients who did not have previous pigmentation (fig. 3). True pigmentation varied from a faint to a deep brown, frequently covered by a thick, dark, waxy coating. Removal of this waxy substance revealed definite pigmentation beneath it. The pigmentation, sometimes limited to the nipple, usually involved the areola

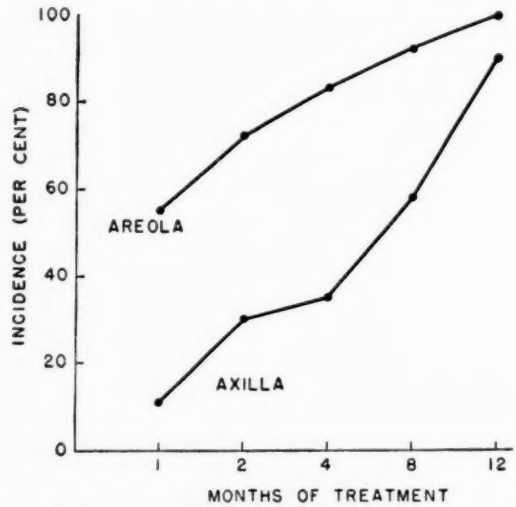

Fig. 4.—Incidence of pigmentation with prolonged estrogen therapy.

and was sharply demarcated at the border. As a rule, the pigment persisted as long as the hormone was administered, although occasionally the color became less intense. After cessation of therapy the pigmentation persisted in some patients for many months. X-ray treatment to the areolar areas usually prevented the formation of pigmentation or destroyed that already present.

During the study, some patients complained that the axillas could not be cleansed. The pigmentation was stippled and was diffuse or confined about the hair follicles in the linear folds (fig. 3). Approximately two-fifths of the patients in this series had axillary pigmentation. The incidence was probably larger, since this aspect was not specifically observed early in the studies. Prolonged estrogen therapy is usually associated with an increased incidence of pigmentation (fig. 4). Pigmentation also occurred in scars as well as in those areas usually affected during pregnancy. Pigmentation was noted in the labia, around or in the umbilicus, and in the linea alba. More recently, pigmentation of the linear lines of the anterior cervical region has been noted. Pigmentation of the buccal mucosa or palms was not seen.

Breast Alterations.—The clinically detectable response of the uninvolved breast tissue to estrogens varied, but it appeared to be governed, to some extent, by the age and menstrual status of the patient. Such signs as tingling or tenderness of the nipples, engorgement, or venous dilatation appeared. Although the group of patients was heterogeneous, about 20% of the entire group exhibited these signs. The changes were confined mostly to premenopausal and menopausal women. Clinical alterations in elderly women, except for pigmentary changes, were considerably less detectable (fig. 5). This implies that the atrophic breast tissue of the postmenopausal and aged woman is not capable of response to the stimuli provided in the prime of menstrual life.

Histological changes may occur without clinical signs, but ordinarily they accompany the overt manifestations.[10] It is quite possible that the status of the breast tissue at the be-

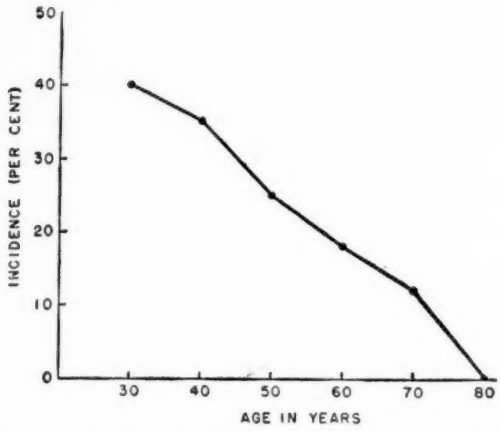

Fig. 5.—Incidence of breast engorgement from estrogen therapy in women with metastatic carcinoma of the breast.

ginning of estrogen therapy may be a determining factor in the responsiveness of the tumor.

Uterine Bleeding.—In contrast to the breast, the postmenopausal endometrium seems to be more sensitive to the action of estrogens regardless of the age of the patient. The latter, however, appears to be a factor in the responsiveness. Large dosages of estrogens produce amenorrhea in premenopausal women with breast cancer, which agrees with observations made in the treatment of patients with other abnormalities.[5a] This is thought to be partially accomplished by inhibition of pituitary gonadotropins, but estrogens may also act directly on the endometrium. These and other studies reveal that intensive estrogen therapy may exhaust the endometrium in its capacity to respond. Continuous and intensive estrogen therapy in postmenopausal patients with breast cancer resulted in uterine bleeding in about one-third of the patients during therapy. The signs consisted of spotting or staining for brief intervals or a flow simulating a normal menstrual period. Generally, no measures were required for control of the bleeding except cessation of the hormone. In some cases, uterine bleeding could also be controlled by sharply increasing the dose of the estrogen. Occasionally, bleeding was sufficiently severe and prolonged to require curettage; the endometriums of the patients subjected to this procedure usually revealed hyperplastic changes. (Prolonged bleeding should lead to the suspicion of stimulated fibroids or cancer of the endometrium.) In younger postmenopausal patients, the bleeding occurred frequently during therapy and almost invariably happened

after treatment was withdrawn. Contrariwise, in elderly women with presumably atrophic endometriums, bleeding was encountered less often during therapy and after withdrawal of therapy. In this latter group, resumption of estrogen therapy resulted in the pattern commonly seen in younger women, for bleeding occurred during the therapy as well as after cessation of the hormone. The incidence of uterine bleeding increased with prolongation of therapy (fig. 6).

These observations prompt the following suggestions: 1. The endometrium, even though apparently atrophic, is sensitive to estrogens many years after the menopause. 2. Once an atrophic endometrium is primed, it responds differently, behaving like that of women in the immediate postmenopausal phase. Generally, however, the incidence of uterine bleeding decreases in successive years after the menopause, both during therapy or after withdrawal (fig. 7). This raises the question of receptivity of the endometrium, which involves blood supply and cellular responsiveness.

Urinary Urgency and Incontinence.—Another effect of large doses of estrogens is frequency and urgency of urination. The urgency of urination is frequently associated with urinary incontinence, usually of the stress type. This was not recognized early in the study because of reluctance of the patients to discuss it. So distressing was the urgency and incontinence that many patients wished to discontinue the medication. Omission of the estrogen was followed by prompt disappear-

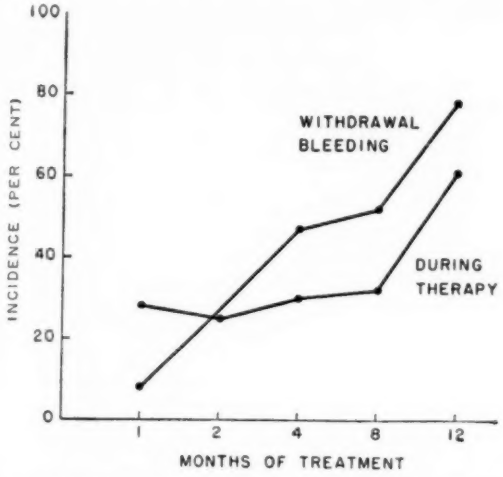

Fig. 6.—Incidence of uterine bleeding after prolonged estrogen therapy.

ance of these symptoms. These urinary symptoms occurred primarily in older women who had borne children. Although the mechanism is not understood, estrogens may affect the sphincter and bladder musculature.

Miscellaneous Effects.—Early in the course of therapy, a few of the patients experienced headaches and dizziness. These symptoms were present in patients receiving larger dosages of estrogens than those usually employed in this program. Cerebral edema might possibly account for these effects. Among other symptoms were drowsiness, "jumpiness," apprehension, lack of "pep," depression, and weakness; these disappeared after treatment was omitted. Increase of libido was reported in a very small percentage of patients.

Occasionally, glossitis, consisting of a bright red, smooth tongue resembling that caused by vitamin B deficiency, developed in patients receiving estrogens. These patients were on a diet apparently adequate in vitamin B complex, but it is possible that the estrogens increase the demand for or suppress the utilization of vitamin B.[11] Improvement followed supplementary vitamin therapy.

Four patients who received estrogens for more than one year had polydypsia and polyuria. Two of these who drank large quantities of fluid a day demonstrated positive tests for diabetes insipidus. Although this disease may possibly be caused by metastases, there was no evidence of this in two patients at autopsy. It can be postulated that the prolonged administration of estrogen may alter the secretion of the posterior pituitary gland.

EFFECTS COMMON TO BOTH ANDROGENS AND ESTROGENS

Extracellular Fluid Retention.—It has been demonstrated that androgens and estrogens produce a decreased excretion and an increased retention of sodium, with a corresponding increase in extracellular fluids.[12] Short-term pilot studies with radioactive sodium in a number of patients revealed an increase in sodium space.

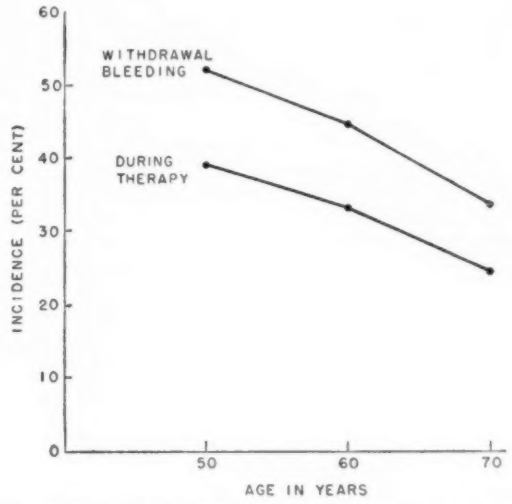

Fig. 7.—Incidence of uterine bleeding, with respect to age, during intensive estrogen therapy and after withdrawal of the hormone.

Early in the course of estrogen or androgen therapy, mild edema, which subsided spontaneously, developed in many patients. Prolonged hormone therapy produced no increase in the incidence of edema; however, a greater incidence of edema was noted in older women, possibly because the cardiovascular system of such patients is less able to cope with the burden of excessive retention of fluid (fig. 8). In the patients treated with massive doses of testosterone, edema of the legs was noted in about one-sixth of the cases. Prolonged estrogen therapy produced peripheral edema in one-third of the patients.

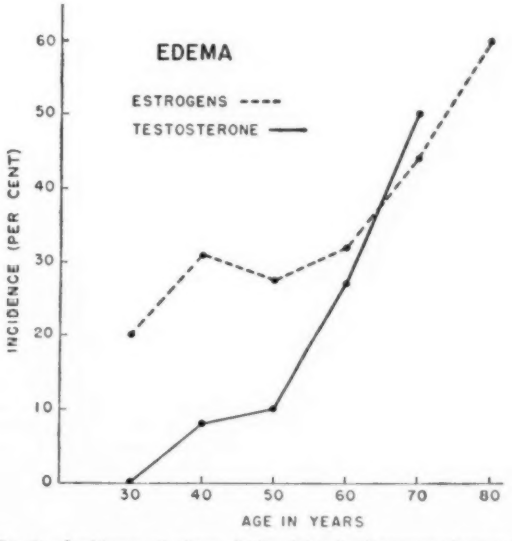

Fig. 8.—Incidence of edema during intensive hormone therapy in women with advanced carcinoma of the breast.

The degree varied from minimal late afternoon swelling to constant edema of the entire legs. Many patients undoubtedly had retention of fluid that could not be detected on clinical examination, because weight gains of 5 to 10 lb. (2.3 to 4.5 kg.) were recorded without gross evidence of edema. Discontinuance of the hormone in a number of patients of this group was usually followed by an obvious diuresis and rapid decrease in weight. These patients did not manifest any renal disease before therapy, as judged by routine urinalyses

or serum nonprotein nitrogen determinations. Existing lymphedema of the arm on the affected side was frequently exaggerated during steroid therapy.

In 17 patients (9%) of those receiving estrogen therapy, fluid retention led to congestive cardiac failure or exaggerated an existing mild decompensation. Five patients who had edema during estrogen therapy died of congestive heart failure at home, according to the family physicians; however, the investigators had not observed any evidence of this condition a short time previously. The breast disease did not appear sufficiently far advanced to cause death. Thus, the incidence of death apparently resulting from congestive failure was recorded as 2.6%. Four cases of acute congestive failure have been reported in men treated with diethylstilbestrol for advanced cancer of the prostate gland. Three of these patients had possible preexisting myocardial damage.[10] Testosterone led to congestive failure in only one member of the present series.

Thrombophlebitis of the lower extremities, which was often unilateral, was prone to occur in women in whom edema developed. It is our impression that this complication happened more frequently than could be expected by chance. Edema, superimposed on poor peripheral circulation, may be an important factor influencing the start of this complication.

TABLE 3.—*Comparative Study of the Incidence of Side-Effects of Synthetic Estrogens*

	Diethylstilbestrol	Conjugated Estrogenic Substance	Dimethyl Ether of Diethylstilbestrol	Ethinyl Estradiol	Dienestrol	Mestilbol
Dose, mg. per day	5 to 400	5 to 30	5 to 30	3 to 5	5 to 30	5 to 30
No. of persons treated	178	23	22	22	14	14
	Incidence of Side-Effects, %					
Anorexia	55.6	43	27	71	58	71
Nausea	56	43	31.8	71	57	71
Vomiting	34.9	23.8	13.6	25	28.5	35.7
Abdominal distress	5	5.6	5	5	14	0
Diarrhea	2.8	11	0	21	0	0
Dizziness	4.5	0	0	0	0	7.7
Headache	8.9	5.9	5.9	0	7.7	0
Drowsiness	7.6	5.9	0	16.7	8	7.7
Libido increase	1.9	0	7.7	0	0	0
Nipple pigmentation	84.7	35.7	78.9	86.7	63.6	83
Areolar pigmentation	78	23	88.9	87.5	70	91.6
Axillary pigmentation	38.6	0	54.5	46	33	50
Scar pigmentation	18.7	0	....	22	0	0
Skin rash	0.9	0	0	7	0	0
Itching	3.9	0	0	0	10	10
Breast engorgement	17	26.7	5.6	25	30	25
Breast tenderness	15	26.7	0	18.7	20	8
Uterine bleeding	34.8	37.5	15.8	6.7	18	35.7
Withdrawal bleeding	41.6	44	33	40	....	33
Urinary symptoms	29	7	7.7	40	42.8	11
Amenorrhea	87.5	....	....	....	....	....
Edema of legs	33	35	26	44	9	28.5
Congestive failure	10	5.9	5	0	0	7
Congestive failure (deaths)	....	5.9	....	....	....	7

Although fluid retention is a serious sequela of androgenic and estrogenic therapy, employment of specific measures will usually control or minimize this complication and in many instances enable continuance of hormone therapy. As a rule, the use of ammonium chloride and a low salt diet are sufficient. If these measures are inadequate, mercurial diuretics can usually correct the situation. Preexisting cardiac failure should be treated before the initiation of hormone therapy. In anticipation of possible fluid retention from steroids, it was our policy to include ammonium chloride and a low sodium intake as a part of the therapeutic regimen in elderly patients or those with known cardiac disease.

Hypercalcemia.—Hypercalcemia may occur with either androgens or estrogens during treatment of advanced breast cancer with osseous involvement.[13] On the basis of blood studies, it was determined that hypercalcemia occurs spontaneously in about 12% of breast cancer patients with osseous metastases.[13c] The number of cases induced by steroid hormones probably is less, but the syndrome is more serious and may be fatal. Spontaneous hypercalcemia may be corrected by steroids, so it does not contraindicate therapy, providing the patient is carefully observed; however, steroid hormones may also induce the syndrome in patients in whom there was no detectable evidence prior to the initiation of therapy. Hypercalcemia was observed in seven (9.6%) of the patients receiving androgenic hormones. Three of these died, apparently as a result of this complication. Hypercalcemia from estrogen therapy was rare in this series, occurring in only two of the total number of patients. Manifestations of hypercalcemia were anorexia, nausea, vomiting, apathy, weakness, drowsiness sometimes merging into disorientation, stupor, or coma, vascular collapse, and, in some instances, death. Although the initial symptoms may be subtle, the syndrome must be suspected in any patient who exhibits these mild symptoms. Serum calcium determinations should be performed at the beginning of and during therapy, especially if suggestive symptoms arise. In addition, the more rapid and simpler estimation of urinary calcium is often informative. Ideally, both assays are desirable. Clinical and laboratory evidence of uremia was present in four of the patients with hypercalcemia who were receiving testosterone. The hypercalciuria apparently produces damage of the renal tubules, with resultant renal insufficiency. Postmortem examination may reveal deposition of calcium in the tubules as well as in other tissues.[14]

The syndrome of hypercalcemia may be corrected, in many instances, by cessation of hormonal therapy, low calcium diet, and infusions of sodium chloride, glucose, and sodium citrate. A 25% solution of sodium citrate can be administered in an amount of 250 cc. intravenously every four hours until improvement occurs. Sodium citrate temporarily reduces the amount of ionized calcium in the blood caused by the formation of a soluble, nonionized calcium citrate complex.[15] However, we believe that correcting the abnormal electrolytic pattern in these patients is most important in treating this serious complication. When drug-induced hypercalcemia is corrected, further steroid therapy may be tried cautiously. The syndrome may recur, but some patients encountered no further difficulty and greatly benefited from the therapy.

Temporary hypercalcemia might have been present in patients noting drowsiness and nausea at the start of therapy, but it was undetected. The incidence of death resulting from hypercalcemia might possibly be reduced by more frequent serum calcium and nonprotein nitrogen determinations and close observation of the patient for early detection of this complication.

Amenorrhea.—Cessation of menstruation is common in women without cancer during treatment with high doses of androgens and estrogens.[5a] Such therapy may produce permanent amenorrhea in women passing through the menopause. Amenorrhea also occurs in menstruating women with disseminated breast cancer who are receiving androgens or estrogens. Of the premenopausal women receiving large doses of estrogenic hormones, 87.5% experienced amenorrhea during this therapy. The hormone-produced amenorrhea can be attributed to suppression of gonadotropic activity, especially since patients resume menstruation after cessation of therapy.[16]

COMPARISON OF NATURAL AND SYNTHETIC ESTROGENS

During the investigation of estrogen therapy in advanced breast carcinoma, both naturally derived and synthetic preparations were employed, in an attempt to evaluate the effectiveness of each. The commonly employed compounds, the average dosages, and the incidence of local and systemic reactions of cases in which synthetic estrogens were used are recorded in table 3. Since these data were compiled, the number of patients treated with compounds other than diethylstilbestrol has substantially increased; however, the relative incidence of reactions has not been altered significantly. At present, the data are insufficient to determine whether any single agent uniformly produces fewer reactions than any other. Further studies with various dosages are necessary to determine the relative incidence of side-effects at each level. No attempt has been made in this report to correlate the various compounds or the systemic reactions with the response of the tumors. The combined use of estrogens and androgens has been tried in a number of patients, but the data are too

few for critical evaluation, especially in respect to effects that are common to both groups of compounds. It appears, however, that more specific sex changes, usually attributed to typical estrogens and androgens, may be minimized with such a combination.

ESTROGENS IN MEN

Large doses of estrogenic hormones have been employed in the treatment of advanced breast cancer in men. Since the series is small, no statistical analysis was attempted. The reactions, which appear similar to those noted in the treatment of prostatic carcinoma, include anorexia, nausea, vomiting, nipple and areolar pigmentation, tenderness and hyperplasia of the uninvolved breast tissue, extracellular fluid retention, and loss of libido; hypercalcemia has not been observed.

SUMMARY AND CONCLUSIONS

Systemic and local reactions were studied in patients with breast cancer receiving intensive sex hormone therapy. A large variety of reactions occurred, which were not specifically related to the action of the hormone on the tumor but could be attributed to inherent qualities of the compounds. This was particularly true when larger dosages were used; they apparently caused a higher incidence of reactions than doses employed in other syndromes. Moreover, at these dose levels, reactions occurred that are not universally recognized.

Further study of the reactions discussed in this report may disclose additional information as to the physiological action of the sex hormones and an explanation of their mechanisms in the treatment of advanced breast carcinoma. Tabulation of the reactions may also contribute to an evaluation of sex steroid hormone therapy in general.

COMMITTEE ON COSMETICS

The following products have been accepted as conforming to the Rules of the Committee on Cosmetics. A copy of the rules on which the Committee bases its action will be sent on application. R. T. STORMONT, M.D., *Secretary.*

Athea Laboratories, Inc.

ATHEA HAND LOTION.—A white emulsion composed of lanolin, petrolatum, a vegetable oil, stearic acid, hexadecanol, magnesium stearate, propylene glycol, cetyl alcohol and perfume, intended to soften and protect the skin. (Bottle: 4 and 8 oz. and 1 gal.)

Cosmetic Laboratories, Inc.

BODY-LO.—A white emulsion composed of liquid petrolatum, polyol esters, a preservative, perfume, color and water, intended to soften and protect the skin. (Bottle: ¼, 3 and 8 fl. oz.)

HAND-LO.—A pink emulsion composed of triethanolamine, colloidal clay, fatty acids and esters, petrolatum, lanolin, alcohol, a preservative, perfume, color and water, intended to soften and protect the skin. (Bottle: ¼, ½, 1, 2, 3 and 8 fl. oz.)

HOMOGENIZED SKIN CLEANSER.—A pale yellow, heavy cream composed of lanolin, a polyol ester, petrolatum, a wax, magnesium sulfate, a preservative, perfume and water, intended to cleanse the skin. (Jar: 1⅞, 3¼, 8½ and 16 oz.)

PROTECTION (OILY, NORMAL AND DRY).—A white emulsion composed of vegetable gums, petrolatum, waxes, soap, borates, benzoic acid, propylene glycol and its stearate, a preservative, perfume, color and water. The ingredients are the same in each of the three forms. The ratio of the ingredients and the perfume content differs in each type. They are intended to keep the skin soft and smooth and to serve as a powder base. (Bottle: 2, 3 and 8 fl. oz.)

Luzier's, Inc.

LUZIER'S LIQUID MAKE-UP BASE.—A pigmented liquid containing glycerin, a fatty acid and its glyceryl and polyethylene glycol esters, an alcohol, a petrolatum, triethanolamine, a surface active agent, a preservative, water and colors, intended to serve as a make-up to provide color to the skin and a smooth appearance. (Bottle: 1 fl. oz.)

Pharma-Craft Corporation

FRESH CREAM DEODORANT.—A white cream composed of basic aluminum formate, aluminum chloride, urea, petrolatum, glycerin, a fatty acid and its glyceryl ester, a suspending agent, perfume and water, intended to temporarily retard the flow of perspiration. (Jar: 0.16, 0.42 0.75 and 1.20 oz.)

HEED DEODORANT SPRAY.—A clear, colorless solution composed of an aluminum chlorhydroxide complex, aluminum chloride, urea, perfume and water, intended to temporarily retard the flow of perspiration. (Plastic Bottle: 1.20 fl. oz.)

SPRITE SPRAY DEODORANT.—A clear, colorless solution composed of an aluminum chlorhydroxide complex, aluminum chloride, urea, alcohol, perfume and water, intended to temporarily retard the flow of perspiration. (Plastic Bottle: 1.5 fl. oz.)

Revlon Products Corporation

AQUAMARINE HAND CREAM.—An aquamarine-colored cream emulsion composed of lecithin, stearic acid, a glycol, glycol ethers and esters, inorganic alkali, a preservative, perfume, color and water, intended to soften and protect the skin. (Jar: 3½ oz. and 1 lb.)

AQUAMARINE LOTION DEODORANT.—An aquamarine cream emulsion composed of polyoxyethylene ethers and esters, cetyl alcohol, cholesterol absorption bases, fatty acid amide derivative, aluminum chlorhydrate, a buffer, a preservative, perfume, color and water, intended to temporarily retard the flow of perspiration. (Bottle: 2¾ fl. oz.)

AQUAMARINE MIST.—An amber-colored solution of essential oils, alcohol, color and water, intended to provide a pleasing scent. (Bottle: 3.12 and 7 fl. oz.)

CAKE ROUGE.—A pigmented cake powder composed of a mixture of talc, glycerin, tragacanth, covering agents, a preservative, perfume and colors, intended to enhance the color of the cheeks. (Cake: 7.8 gm.)

CHEEKSTICK.—A pigmented, waxy solid in stick form, composed of petrolatum, lanolin, a wax, a covering agent, a preservative, perfume and colors, intended to enhance the color of the cheeks. (Stick: 2.6 gm.)

CUTICLE OIL.—A rose-colored solution composed of petrolatum, color and perfume, intended to soften the cuticle. (Bottle: 1 and 4 fl. oz.)

CUTICLE REMOVER.—An off-white solution of a polyethoxy ether, a substituted ammonium hydroxide, propylene glycol, a preservative, a color and water, intended to soften the cuticle and permit its removal by gentle friction. (Bottle: 1, 4 and 16 fl. oz.)

DESTINA MAKE-UP REMOVER.—A clear green solution composed of a polyoxyethylene ester, alcohol, glycerin, perfume, colors and water, intended to facilitate the removal of make-up. (Bottle: 4 fl. oz. and qt.)

EYEBROW PENCIL.—A pigmented waxy solid composed of fatty acids, lanolin, waxes, a vegetable oil, glycerides, a resin and colors, intended to enhance the color of the eyebrows. (Pencil: 1⅜ in. by 0.115 to 0.120 in.)

HAND COLOGNE.—A clear pink solution composed of alcohol, polyethylene glycols, perfume, colors and water, intended to provide a pleasing scent. (Bottle: 4 and 16 oz.)

INDELIBLE CREAM LIPSTICK.—A waxy solid stick composed of waxes, glycol and a glycol ester, vegetable oils, a cholesterol absorption base, a covering agent, a preservative, perfume and colors, intended to enhance the color of the lips. (Tube: 4.5 gm.)

NAIL CREAM.—A pink cream composed of lanolin, petrolatum, a sorbitan ester, a wax, a covering agent, perfume, color and water, intended to soften the cuticle. (Jar: ½ and 2 oz.)

NIGHT HAND CREAM.—A thick pink cream composed of petrolatum, lanolin, a cholesterol absorption base, a preservative, perfume, colors and water, intended to soften and protect the skin. (Jar: 2¼ oz.)

PASTE POLISH.—A pink cream composed of a wax, a phthalate ester, lecithin, covering agents, perfume and color, intended to add gloss to the nails. (Jar: 0.95 oz.)

PINK LACTOL.—A thick pink cream lotion composed of a fatty acid and its ester, alcohols, triethanolamine, lanolin, preservatives, perfume, colors and water, intended to soften and protect the skin. (Bottle: 32 and 128 fl. oz.)

TOUCH AND GLOW.—A pigmented liquid composed of stearic acid, and its glycol ester, cholesterol bases, lecithin, covering and thickening agents, triethanolamine, a glycol, preservatives, perfume, colors and water, intended to serve as make-up to provide color to the skin and a smooth appearance. (Bottle: 1 and 2 fl. oz.)

Shepard Laboratories

SHEPARD'S CREAM LOTION.—A white emulsion composed of glycerin, a fatty acid and its glyceryl ester, triethanolamine, cetyl alcohol, preservatives, propylene glycol, carbitol, alcohol, sesame oil, perfume and water, intended to soften and protect the skin. (Bottle: 8 fl. oz.)

SHEPARD'S COLD CREAM.—A white heavy cream composed of waxes, petrolatum, a glyceryl ester, cetyl alcohol, a preservative, sodium borate, perfume and water, intended to cleanse the skin. (Jar: 3½ oz.)

SHEPARD'S DRY SKIN CREAM.—A yellow cream composed of a wax, lanolin, petrolatum, and perfume, intended to relieve skin dryness. (Jar: 1½ oz.)

Toni Company

TONI HOME PERMANENT (VERY GENTLE, REGULAR AND SUPER).—A creamy solution consisting of ammonium thioglycolate, free ammonia, ammonium salts, an emollient creaming agent, a surface active agent, perfume, color and water. This is provided in three strengths, very gentle, regular and super, intended for easy-to-wave, normal and hard-to-wave hair, respectively. This is a cold waving solution intended to be used with a chemical neutralizer. (Waving Lotion: 4 fl. oz.)

PROM HOME PERMANENT (VERY GENTLE, REGULAR AND SUPER).—A creamy solution consisting of ammonium thioglycolate, free ammonia, ammonium salts, an emollient creaming agent, a surface active agent, perfume, color and water. This is provided in three strengths, very gentle, regular and super intended for easy-to-wave, normal and hard-to-wave hair, respectively. This is a cold waving solution intended to be used without a chemical neutralizer. (Waving Lotion: 4 fl. oz.)

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WATCH IT, *LIFE*

Physicians read with amazement and resentment the recent editorial, "Watch It, Doc," which appeared in the June 22, 1953, issue of *Life* magazine.

The editorial condemned the action of the House of Delegates of the American Medical Association for adopting a resolution presented by delegates of the Indiana State Medical Association pertaining to the care of crippled children.

It is unfortunate that *Life's* editors apparently took neither the time nor the trouble to investigate the facts before sounding off on a subject so close to the hearts of millions of its readers.

Indiana was the first state to tell Washington to keep its general welfare money, pledging to carry on its own program without a 20 million dollar federal handout. This was brought about by the action of the state legislature in passing an antisecrecy clause to reduce the rapidly rising cost of welfare in Indiana by opening the reports of the state's department of welfare to public view. This movement spread rapidly throughout the country, and it took an act of Congress to protect the various states from reprisals by the Federal Security Agency, which was then headed by Oscar Ewing.

The editorial gave a distorted picture not only of the position of the A. M. A. House of Delegates but also of the actions of the New York County Medical Society concerning the extension of medical care to a housing project proposed by the New York State Housing Commissioner. Judging from the reference to the medical care housing controversy, *Life's* writer must have been content to use only newspaper clippings and secondhand sources of information.

Life has violated one of the cardinal principles of good journalism—the accurate reporting of facts. The New York County Medical Society said in a letter to *Life's* chief editorial writer:

"*Life* repeated—with damaging effect—a quotation attributed to our chairman of the Committee of Medical Economics, which first appeared in the *New York Times* on April 7, 1953, about giving the patients 'breakfast in bed.' This was categorically denied to the *New York Times* on the same date but your writer, using only newspaper clips and not coming to the Society for his information, repeated the libelous phraseology and compounded it by going on to comment about Marie Antoinette and 'let them eat cake.' "

If *Life* had taken the time New York and other newspapers did to check the facts behind the crippled children's resolution, an entirely different picture would have been unfolded. The facts underlying introduction of the resolution before the A. M. A. House of Delegates and the subsequent action by the House are in keeping with the demand of the public for a sensible form of government administration of various assistance programs. The resolution pertained to a regulation adopted by the Federal Security Agency in 1944 under Paul V. McNutt, Federal Security Agency Administrator, which reads:

"Section 200.9 of Part 12-4 of Regulations for Maternal and Child Health and Crippled Children's Program, entitled 'Crippled Children's Programs: Diagnostic Services.'

"State plans for Crippled Children's Services shall provide that the diagnostic services under the plan will be made available within the area served by each diagnostic center to any child (a) without charge, (b) without restriction or requirement as to the economic status of such child's family or relatives or their legal residence, and (c) without any requirement for the referral of such child by any individual or agency."

Before a state can obtain federal approval for its crippled children's program it must adopt this regulation or at least the sense of it. States are compelled to renew the crippled children's pledge set forth in the Federal Security Agency regulation every two years. With a change of administration in Indiana, a new welfare board was confronted with accepting the provisions by July 1, 1953, or failing to have the welfare program approved under the law. Eventually, Indiana's welfare board, under coercion, reluctantly approved the regulation for a two year period, but lodged a vigorous protest with Washington, saying the approval was being given under protest.

Life never touched on this background, nor does it appear to have consulted the Indiana Department of Public Welfare, which recently reported that the state's crippled children's program was costing the taxpayers almost nothing—thanks to a long-time arrangement with Indiana physicians who contribute their professional services. To *Life,* this apparently means nothing. Had the magazine checked its facts, it would have learned that Indiana's director of the crippled children's program recently praised physicians of that state for willingly treating deserving crippled children on other than a fee-for-service basis.

Life could have learned, too, if it had taken the time, that Indiana taxpayers are paying the physicians in the program an honorarium averaging only $40 per month or $480 per year for all professional services to crippled children in the state. For this amount, which totals less than $10,000 per year, the children receive professional services that would cost more than $100,000 per year on a fee-for-service basis, according to the state's welfare department.

In reporting for the year 1952, the Indiana Department of Public Welfare's figures show that during the calendar years, Indiana physicians treated 2,844 children in clinic and made a total of 9,354 visits. In addition, 655 children received a total of 15,857 days of

corrective hospital care by physicians, or an average of 24 days per child, for which the physicians received no extra pay for visits or services. Another 2,517 children received auxiliary orthopedic and therapy services in their home communities as a follow-up precaution to make sure that each child was being properly rehabilitated.

Such services to crippled children are not given in Indiana alone. Every Shriner hospital ward, orthopedic hospital, county hospital, and private hospital can certify to similar charitable services by physicians in every state in the union. It has never been the intent of the medical profession to remove the availability of medical care from those who are in need of care and unable to pay.

In introducing the resolution to the A. M. A. House of Delegates, Indiana physicians believed honestly and sincerely that whenever any law or regulation provides free service for all, regardless of economic status, and whenever the responsibility of control is removed from a state or local agency charged with the responsibility of administering and paying for the services performed, it definitely is a socialistic program.

It is significant that *Life* chose to ignore all the other resolutions acted on by the House of Delegates—many of them dealing with constructive and positive aspects of the American Medical Association's program—and elected to concentrate on one to which wide interpretation and speculation could be given. As Dr. Louis H. Bauer said in a letter to *Life*: "You took one resolution adopted by the House of Delegates and distorted the action of the House." He charged the magazine with exhibiting "either woeful ignorance or an unwillingness to accept fact."

Magazines and newspapers have ethics the same as the medical profession. In reporting on the A. M. A. action, *Life* threw the fundamental canons of journalism —sincerity, truthfulness, and accuracy—out the window. In doing so, *Life* betrayed not only the physicians of this country but also its big family of readers. Good faith with the reader is a paramount principle. By every consideration of good faith, a magazine is constrained to be truthful. It is not to be excused for lack of thoroughness or accuracy within its control. So, in reply to *Life's* "Watch It, Doc," one can say "Watch It, *Life*."

REDUCTION OF MOTOR VEHICLE DEATHS AN INDIVIDUAL RESPONSIBILITY

A total of 262 persons lost their lives in motor vehicle accidents in the United States during the Fourth of July weekend this year. Most of these lives were lost needlessly. It is ironic that with the millions of dollars and thousands of man-hours spent for medical research to prolong human life each year, almost a million persons sacrifice their lives and limbs through carelessness on the highways. Although the death rate from disease has decreased during the last decade, flagrant violations of highway safety rules have resulted in a constantly increasing death and injury rate from motor vehicle accidents.

During the first five months of 1953, 14,230 persons were killed in motor vehicle accidents in the United States, a 4% increase over the 13,740 persons killed during the same period of time in 1952. According to "Accident Facts," published yearly by the National Safety Council, in 1952 motor vehicle accidents in the nation resulted in 38,000 deaths, caused injuries to 1,350,000 persons, and cost $3,750,000,000. There were 33,000 fatal accidents, 900,000 nonfatal injury accidents, 3,400,000 accidents causing property damage of $25 or more, and 5,200,000 accidents causing property damage of less than $25.

Seven out of 10 motor vehicle deaths in 1952 occurred in rural accidents, and more than half of all deaths occurred at night. Nearly one-fourth of the fatally injured were pedestrians. Collisions between motor vehicles were mostly head-on and sideswipe crashes. The principal noncollision accident was running off the roadway at curves.

Excessive speed was the most important driver violation. Nationally, 28% of the drivers in fatal accidents were driving too fast for traffic, weather, and/or road conditions, even though they may not have been exceeding a legal speed limit. In urban areas, right of way violations were second in importance; in rural areas, failing to keep right of the center line was second.

In 23 out of 100 fatal accidents, a driver or a pedestrian had been drinking; 10 out of 100 drivers or pedestrians had some bodily defect. Adverse weather was reported in one out of four fatal accidents, while 6% of vehicles involved in fatal accidents had one or more unsafe conditions; in nearly one out of eight fatal accidents, the driver's vision was obscured. Two out of five fatal accidents occurred on Saturday and Sunday.

Reduction of the ever-increasing motor vehicle death rate is everyone's responsibility. Most motor vehicle accidents are avoidable. The person behind the wheel of the automobile is responsible not only to himself but to all others for observing all speed laws and traffic signs, for maintaining his vehicle in proper working order, and for making certain that he is in proper physical and mental condition to operate the vehicle. He must observe not only the road and persons directly ahead of him, but he must be cognizant of traffic and pedestrians on either side of and behind him. Pedestrians also are individually responsible for reducing the death rate from motor vehicle accidents. They must observe all safety rules and regulations designed for their protection.

Physicians have a unique position in the prevention of motor vehicle accidents. They are able to work with individuals and organizations in an advisory capacity to ascertain when a person should or should not drive an automobile. If a physician has a patient who, for one reason or another, should not operate a motor vehicle, it is his duty to proffer such advice. A physician should not wait until a patient asks him if he can drive an automobile; the majority of persons will not seek such counsel. Such advice may save a life—and the life may be that of someone dear to the physician or the patient.

Certain conditions are contraindications for operating a motor vehicle, and physicians are best informed about them. Individual evaluation as to whether or not a person should drive an automobile should be made of persons

who have just had certain types of physical examinations or who have just received an anesthetic; of persons taking certain drugs such as antihistamines and sedatives; of persons with mental instability, uncontrolled diabetes, and certain forms of epilepsy; and of persons with heart disease or severe hypertension.

Only by assumption of such individual responsibility can the death rate from motor vehicle accidents be reduced. Such accidents are unnecessary; they can and must be abated. In such a program physicians everywhere can be and should be helpful.

RELIEF FROM RAGWEED

The control of unwanted vegetation that harbors insects, blisters the skin, or produces undesirable types of pollen has been largely unsuccessful because of the lack of convenient and relatively inexpensive means of eradicating the offending plants. The widespread distribution of pollen-producing weeds such as various species of Ambrosia (ragweed) and skin-irritating vines, bushes, and shrubs of the genera of Toxicodendron (poison ivy, sumac, and oak) has been one of the principal obstacles to successful management of seasonal allergic rhinitis and contact dermatitis due to these causes. The introduction of selective herbicides has renewed interest in the control of these and other noxious plants.

The most widely heralded herbicide development of the past decade was the public announcement in 1944 of the growth-regulating properties of 2,4-dichlorophenoxyacetic acid (2,4-D). Weed control through growth regulation marked a new departure in herbicides and offered one of the most promising methods for eliminating noxious vegetation such as ragweed and plants of the genus Toxicodendron. Through health education and community organization the removal of these plants in urban and other frequented areas is now both possible and practical.

Ragweed is among the more sensitive of common weeds to 2,4-D, and pollen formation may be prevented by the use of spray and fog methods of dispersion. Destruction of ragweed should be undertaken in the early part of August so as to prevent the shedding of pollen and the dropping of seeds. 2,4-D is most effective on poison ivy around the end of the growing season, when large leaf surfaces are presented to the action of the chemical. A subsequent spraying a month later may be necessary for those plants surviving the initial treatment; however, use of the growth-regulant late in the season is not recommended, because the plants are dormant and largely unaffected by the material.

While 2,4-D is noncorrosive, nonexplosive, and noninflammable, caution must be taken when using it in the vicinity of cultivated plants. It attacks most broad leaf plants and is effective in exceedingly small amounts (10 ppm or less). Care must be taken to avoid drifting of spray dust or fumes to flowering plants and fruit trees in the vicinity of spraying. Spray equipment must also be thoroughly decontaminated by washing with alkali or kerosene to remove residual chemical remaining after use of aqueous and oil sprays. Although sensitivity may be experienced by persons sensitive to compounds of the phenolic type, 2,4-D is comparatively harmless to animals and humans. It is not irritating to the skin except in concentrated forms, although the petroleum products used in certain formulations may be a cause of complaint. The dusts of 2,4-D can be irritating to the eyes and respiratory tract, and precautions against this should be undertaken during application.

Various formulations of 2,4-D are available under a variety of trade names. The label accompanying each product provides a statement of composition as well as complete instructions for application. The directions for use should be scrupulously followed if full benefit from the compound is to be obtained.

CANCER AS A CHRONIC DISEASE

Numerous case reports indicating the unpredictability of cancer as a disease are scattered throughout the medical literature. It has been observed that in any series of untreated cancer patients certain patients will have a much longer survival rate than the average, with some tumor types disappearing spontaneously and others seemingly growing in cycles, with periods of rapid growth alternating with stationary periods or actual recessions. Moreover, the phenomenon of delayed recurrence has been observed, wherein the tumor reappears years later either in the scar that has been produced by previous surgical intervention or in the surrounding area. Occasionally, metastatic cells appear dormant in lymph nodes and other vital structures of the body without ever producing symptoms; sometimes, however, rapid metastasis occurs throughout the body after a prolonged period of quiescence.

Morton and Morton [1] recently summarized their experiences with a group of 17 cases of cancer that originated in various organs, including the thyroid gland, neck, breast, orbit, parotid gland, and the kidney. These cases were unusual in that the patients had prolonged periods of active, useful life, even though the malignant disease had not been completely eradicated by surgical means. They point out that cancer may behave as a chronic disease for more than a quarter of a century, that there is wide variation in the individual resistance of patients to malignant growths, and that chronicity is not confined to any particular type of cancer. In view of the absence of a completely acceptable explanation for the prolonged survival rate of some patients afflicted with cancer, there is need to be cautious in estimating the survival rate of patients when offering a prognosis to patients and their families. Furthermore, prolonged and sometimes unexplainable periods of survival after diagnosis of cancer reveal why some so-called cancer treatments are accorded at least temporary support.

1. Morton, J. J., Jr., and Morton, J. H.: Cancer as a Chronic Disease, Ann. Surg. **137**: 683 (May) 1953.

ORGANIZATION SECTION

OPINION SURVEY AND INVENTORY OF MEDICAL CARE, PERSONNEL, AND FACILITIES IN MECKLENBURG COUNTY, NORTH CAROLINA

David G. Welton, M.D., Charlotte, N. C.

Early in 1951, a special study committee [1] was appointed by Dr. Monroe T. Gilmour, then president of the Mecklenburg County Medical Society, to determine the facts about medical care in Charlotte and Mecklenburg County, North Carolina. To make this community study comprehensive in scope, the society invited representatives of the dentists, nurses, Negro physicians and dentists, public health departments, and hospitals to participate. All responded. The public was represented by an outstanding civic leader who was director of public libraries within the county.

So far as known, the opinion survey portion of this study was the first of its type done in the South; it was also the only one done in the United States that included a significant Negro representation—of 29%—and that was conducted as part of an inventory of medical facilities. Five hundred residents, in a cross section sample, were personally interviewed.

PUBLIC OPINION FINDINGS

The highest praise for medical services was given to the availability of surgeons when 97% of those interviewed and who expressed an opinion said that they had no difficulty securing the services of surgeons. The availability of doctors was rated next, with 90% stating they had no difficulty securing services; availability of nurses next, with 88%; availability of dentists next, with 86%; and availability of hospitals next, with 85%.

Seventy-two per cent of those who expressed opinions said they thought doctors' charges were fair; this proportion was 5% less than of those who said nurses' charges were fair. Sixty-four per cent said surgeons' charges were fair, and an identical percentage said the same about dentists' charges. Drug bills and hospital bills scored lower. Sixty-one per cent with opinions said drug bills were fair, and 49% said hospital bills were fair.

When persons in Mecklenburg county, however, were asked "Do you think it is proper to ask what the charges will be before engaging the services" of doctors, surgeons, dentists, drug stores, hospitals, and nurses, they replied 64% no for drug stores; 58% no for doctors; 34% no for dentists; 28% no for hospitals; and 20% no for surgeons and nurses.

Although 85% or more of those interviewed who expressed an opinion praised the availability of each one of the medical services, their percentages of favorable responses were much smaller when they were asked if they thought there is a shortage of medical personnel and facilities. Eighty-six per cent said there was a shortage of hospitals, and 70% said there was a shortage of nurses. Sixty per cent said there was a shortage of doctors; 44% said there was a shortage of dentists; 34% said there was a shortage of surgeons; and 15% said there was a shortage of drug stores. The survey showed that 80% of the families in the county have a family doctor. Sixty-seven per cent have a family dentist; 63% have a family drug store; and 43% have a family surgeon and a family hospital. Only 2% have a family nurse.

Eighty-five per cent with opinions said their family doctor makes house calls willingly. But only 61% of those interviewed knew about the Medical Emergency and Information Service operating in Charlotte that gives out medical information and obtains doctors for emergency calls.

Eighty per cent with opinions said they would like itemized statements from doctors. Thirty-seven per cent said they thought their doctor would charge more if he knew they had medical insurance.

A lack of information about doctors' overhead costs was revealed when those with opinions—and only 34% of those interviewed had them on this question—estimated that their doctor on the average pays only 14.2% of his income for professional and office expense. The national average for overhead for doctors is actually 41 cents out of every dollar taken in. The overhead estimate for dentists averaged 11.4%, whereas the national average is 45%. Only 29% of those interviewed ventured an opinion on the percentage of work time given by doctors to the care of charity patients. They estimated on the average 18.5% for physicians and surgeons. The 20% with opinions estimated 7.1% for dentists. Slightly more than half, 52% of those holding opinions, thought that doctors' charges have increased as much as food. The 1951 Consumers' Price Index and Price Indexes for Medical Care show instead that, while the fees of the general practitioner, surgeon, and specialist in large cities have gone up 45.2%, food prices have risen in these same cities 127.4% over the 1935-1939 average.

Seventy-one per cent of those interviewed said they carried hospitalization insurance. Eighty-five per cent of those with opinions said they thought that public tax funds should be used to pay for hospitalization of those unable to pay. Seventy-five per cent said they favored merging city and county health departments, but only 60% said they favored merging city and county governments. Only 53% of those interviewed had opinions about the merging of local health departments, and only 49% had opinions about merging of local governments.

THE AREA SURVEYED

Interviews were conducted in Charlotte, Davidson, Cornelius, Matthews, Huntersville, Pineville, and in rural Mecklenburg County late in 1951 and early in 1952. Charlotte is the largest city in the Carolinas, with a recorded population of 135,000. Sixty-five thousand additional persons reside in the rest of Mecklenburg County surrounding Charlotte, making a total county population of 200,000. Approximately 65% are native-born white persons and 35% are Negroes, with less than 1% being foreign born.

The average per family income in Charlotte was $5,500 in 1950. In the heart of the Piedmont region of the Carolinas, there are more than 650 textile mills within a 100 mile radius of Charlotte, which has served as the medical center for this area for more than 50 years.

There are 225 available physicians, 65% of whom are board-certified specialists. Dentists number 84, graduate nurses 792, and hospital beds, 1,032.

THE METHOD

Proportionate representation of high, middle and low income groups, and varied age, sex, racial, educational, occupational, urban, and rural groups was achieved in the sample. The interviewing was done by Mrs. Olga Porter, formerly of Charlotte, a trained interviewer, with experience on surveys for the University of North Carolina and numerous business organizations. Because the society did not have the facilities for properly tabulating and analyzing the survey findings, it appealed to the American Medical Association for assistance. As a result, Lawrence W. Rember, Director of Field Service

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President, Mecklenburg County Medical Society.

Mr. Lawrence Rember, Director of Field Service, Department of Public Relations, American Medical Association, assisted in preparing the section on public opinion findings and in condensing the original report.

1. Members of the Study Committee of the Mecklenburg County Medical Society were, 1951 and 1952, Dr. David G. Welton, Chairman; Dr. William T. Raby, Vice Chairman; Dr. Andrew Taylor, Secretary; 1951, Dr. Gregg Watters; 1952, Dr. Addison Brenizer Jr., Research; Dr. Ralph Bell, Physician Personnel; Dr. Z. Vance Kendrick, Charlotte Dental Society; Miss Ann Rhodes, District Nurses Association; Dr. M. B. Bethel, City and County Health Services; Dr. Rudolph M. Wyche, Negro Physicians and Dentists; Mr. Marshall Pickens, Hospital Facilities; and Mr. Hoyt Galvin, the Public. The Advisory Group were Drs. Hamilton McKay, V. K. Hart, Luther Kelly, H. L. Newton, Monroe T. Gilmour, ex-officio, 1951, and E. R. Hipp, ex-officio, 1952.

for the Department of Public Relations, came to Charlotte to consult with the society and to extract and to write the reports for release to the public. Keying and tabulating of the data was done under the direction of Dr. Frank Dickinson, head of the Bureau of Medical Economic Research of the A. M. A. Question by question, the results to the 27 statistical questions of the survey follow:

FAMILY MEDICAL RELATIONSHIPS

1. *Do you have a family doctor?*

Yes	80%
No	20

Only 43% of those interviewed said they had a family surgeon. Only 43% said that they had a family hospital, indicating that the majority of persons go where their doctor or surgeon recommends or where there is an available bed. Only 2% said they had a family nurse.

2. *Do you have a family dentist?*

Yes	67%
No	33

3. *Do you have a family drug store?*

Yes	63%
No	37

AVAILABILITY OF MEDICAL CARE

4. *Do you have trouble securing the services of doctors?*

Yes	9%
No	88
No answer	3

Of those who did express an opinion, 10% said they had trouble securing the services of a doctor and 90% said they did not. Of the 89% who expressed an opinion on securing the services of surgeons, 3% said they had trouble and 97% said they did not. Of the 94% who expressed an opinion on securing the services of hospitals, 15% said they had trouble and 85% said they did not. Of the 84% who expressed an opinion on securing the services of nurses, 12% said they had trouble and 88% said they did not.

5. *Do you have trouble securing the services of dentists?*

Yes	13%
No	83
No answer	4

Of those who did express an opinion, 14% said they had trouble securing the services of a dentist and 86% said they did not.

6. *Do you have trouble securing the services of drug stores?*

Yes	1%
No	99

QUANTITY OF MEDICAL CARE

7. *Do you think there is a shortage of doctors?*

Yes	53%
No	35
No answer	12

Of those who did express an opinion, 60% said they thought there was a shortage of doctors and 40% said they thought not. Of the 71% who expressed an opinion on whether or not there is a shortage of surgeons, 34% said they thought so and 66% said they thought not.

Of the 90% who expressed an opinion on whether or not there is a shortage of hospitals, 86% said they thought so and 14% said they thought not. Of the 74% who expressed an opinion on whether or not there is a shortage of nurses, 70% said they thought so and 30% said they thought not. The percentages of persons expressing a considerable belief that there is a shortage of doctors, hospitals, and nurses are in marked contrast to the answers given by respondents to parts of question 4, in which a high percentage said they had had no trouble securing these medical services.

North Carolina now has three four-year medical schools; within another two years, a total of about 175 physicians will be graduated annually from these three schools. A newly established school of dentistry at the University of North Carolina will soon be graduating approximately 50 dentists each year.

8. *Do you think there is a shortage of dentists?*

Yes	36%
No	45
No answer	19

Of those who did express an opinion, 44% said they thought there was a shortage of dentists and 56% said they thought not.

9. *Do you think there is a shortage of drug stores?*

Yes	14%
No	81
No answer	5

Of those who did express an opinion, 15% said they thought there was a shortage of drug stores and 85% said they thought there was not.

ASKING CHARGES BEFORE ENGAGING SERVICES

10. *Do you think it is proper to ask what the charges will be before engaging the services of doctors?*

Yes	42%
No	58

Eighty per cent of those interviewed said that they thought it was proper to ask the surgeon what he would charge before engaging his services. The percentage was the same regarding nursing service, and 72% said the same thing about hospital services.

11. *Do you think it is proper to ask what the charges will be before engaging the services of dentists?*

Yes	66%
No	34

12. *Do you think it is proper to ask what the charges will be before engaging the services of drug stores?*

Yes	36%
No	64

FAIRNESS OF CHARGES

13. *Do you think the charges that doctors make are fair?*

Yes	65%
No	25
No answer	10

Of those who did express an opinion, 72% said they thought that doctors' charges were fair and 28% said they thought they were not. Of the 58% who expressed an opinion on the fairness of surgeons' charges, 64% said they thought the charges were fair and 36% said they thought not. Of the 80% who expressed an opinion on the fairness of hospital charges, 49% said they thought the charges were fair and 51% said they thought not. Of the 52% who expressed an opinion on the fairness of nurses' charges, 77% said they thought the charges were fair and 23% said they thought not.

14. *Do you think that the charges which dentists make are fair?*

Yes	56%
No	31
No answer	13

Of those who did express an opinion, 64% said they thought that dentists' charges were fair and 36% said they thought not.

15. *Do you think the charges that drug stores make are fair?*

Yes	54%
No	35
No answer	11

Of those who did express an opinion, 61% said they thought that drug stores charges were fair and 39% said they thought not.

16. *Do you think doctors' charges have increased as much as food costs?*

Yes	43%
No	40
No answer	17

Of those who did express an opinion, 52% said they thought that doctors' charges have increased as much as food costs and 48% said they thought not. The actual increase over the 1935-1939 average is 45% for doctors' charges and 127% for food prices.

17. *Do you think your doctor charges more when he knows you have medical insurance?*

Yes	28%
No	48
No answer	24

Of those who did express an opinion, 37% said they thought that their doctor charges more when he knows they have insurance and 63% said they thought not.

LOCAL GOVERNMENT PARTICIPATION

18. *Do you think public tax funds should be used to pay for hospitalization for those unable to pay?*

Yes	76%
No	13
No answer	11

Of those who did express an opinion, 85% said they thought public tax funds should be used to pay for hospitalization of the needy and 15% said they thought not.

19. *Do you favor merging city and county health departments?*

Yes	40%
No	13
No answer	47

Of those who did express an opinion, 75% said they favored merging city and county health departments and 25% said they did not.

20. *Do you favor merging city and county governments?*

Yes	29%
No	20
No answer	51

Of those who did express an opinion, 60% said they favored merging city and county governments and 40% said they did not. It is clear here that an education job needs to be done to inform more citizens about the advantages of such mergers. The significant finding here is that such a large percentage had no opinion at all.

INCOME OF DOCTORS

21. *Would you like itemized statements from doctors?*

Yes	72%
No	18
No answer	10

Of those who did express an opinion, 80% said they would like itemized statements from doctors and 20% said they would not.

22. *What percentage of the full income would you estimate is paid for professional and office expense by your doctor? By your dentist?*

	Doctor	Dentist
Public's estimate	14%	11%
Actual	41	45

The highest estimate of the 34% and 31% of persons, respectively, who expressed an opinion was 75% and the lowest estimate was 1%, showing an extreme range of opinion and a considerable lack of information about doctors' and dentists' overhead costs.

23. *What percentage of work time do you estimate is given to charity patients by doctors? By dentists?*

Doctors	19%
Dentists	7

The highest estimate of the 29% expressing an opinion in regard to doctors was 60% and the lowest estimate was 0%. The highest estimate of the 20% expressing an opinion in regard to dentists was 40% and the lowest estimate was 0%.

HOSPITALIZATION INSURANCE

24. *Do you carry hospitalization insurance?*

Yes	71%
No	29

25. *Do you carry Blue Cross?*

Yes	34%
No	37

HOUSE CALLS

26. *Does your family doctor make house calls willingly?*

Yes	66%
No	12
No answer	22

Of those who did express an opinion, 85% said their family doctor makes house calls willingly and 15% said he did not.

27. *Do you know about Medical Emergency and Information Service operating in Charlotte and Mecklenburg County?*

Yes	61%
No	39

VERBATIM COMMENTS

In addition to the answers that were given to the 27 statistical questions, verbatim comments and criticisms were solicited from the residents of Mecklenburg County as to what they thought was wrong with their doctors, hospitals, dentists, and health departments. Residents of Mecklenburg were asked also to make suggestions for the improvement of medical care.

The five comment questions were so worded that they requested and encouraged the expression of criticism rather than praise, since the main purpose of the survey was to obtain suggestions for the improvement of medical care in Charlotte and Mecklenburg County and not laudations of its virtues. Among the comments, nevertheless, were many a commendation. Where the respondent volunteered a compliment, it, too, was recorded.

Less than 50% of the citizens who were interviewed had any kind of unfavorable criticism. Out of a total representative sample of 500 interviews, 49% expressed a criticism about hospitals, 46% about doctors, 20% about dentists, and 7% about the health department. The remainder of those interviewed apparently were satisfied with the medical care that they were receiving. At least they had no criticism to offer.

WHAT THEY SAID ABOUT DOCTORS

Criticism of doctors centered mostly around refusal to make house or night calls and high fees and then dropped sharply for the other complaints. Eighty-eight per cent of the doctor criticisms fell into the following 10 categories:

	No. of Criticisms
Refusal to make house or night calls	105
Extreme or too high fees	46
Long waiting period and lack of definite appointments	24
Slow responses to house calls	22
Mercenary attitude	15
Too much specialization and not enough family doctors	14
Fees based on ability to pay or greater after 6 p. m. or midnight	12
Attitude too professional, cold, impersonal	12
Too hurried or too busy	12
Demand that patient come to hospital and too much telephone diagnosis	10

The various remaining criticisms about doctors received five or less mentions out of the total of 500 persons interviewed. Slightly more than one person out of two expressed no criticism of doctors.

ABOUT HOSPITALS, DENTISTS, AND HEALTH DEPARTMENTS

The main criticisms of hospitals were made in this descending order: need more hospitals and hospital space; not enough doctors, nurses, and general personnel; impersonal and hurried service; too mercenary an attitude; inefficient management and help; and unappetizing or insufficient food; too strict in visiting or other rules; lack of cleanliness; and slow emergency attention and admittance procedures. Not quite one out of every two persons expressed a criticism of hospitals.

The main criticisms about dentists were high fees and long waiting for appointments. Only one out of every five persons expressed criticism of dentists.

As for the city health department, many persons were unaware of its existence or activities. The 7% who did have complaints to offer scattered their criticisms over so many different categories that no one type of complaint was made

by more than 4 persons out of 500. Only one out of every 14 persons expressed any criticism about the city health department.

SUGGESTIONS FOR IMPROVING MEDICAL CARE

Although all of those interviewed were asked to make suggestions for the improvement of medical care, only 63% had a suggestion to offer. Five hundred and five improvement suggestions were made by 315 persons.

The gist of what they suggested was "more": more hospitals, more doctors, more nurses, more interns and residents, more clinics, and more of other things.

Here is how they would improve medical care:

	No. of Suggestions
More hospital space, more facilities, or more hospitals	105
More doctors and family doctors	87
More house calls by doctors	74
More nurses and personnel	46
More immediate emergency care and less admittance red tape	21
Less mercenary attitude and lower rates	20
More personal doctor-patient basis	19
Better and more considerate service for charity patients	18
More interns and resident doctors	13
Increased effort for adequate insurance	13
More free and low-fee clinics	10
Less telephone diagnosis	8
Charge according to ability to pay	7
Shorten office waiting time	7
Less specialization	6
More doctors, interns and facilities in hospitals at night	4

Ninety-one per cent of the suggestions were made in these 16 categories. The remaining 9% were divided among 33 other types of suggestions, none of which received more than three mentions and most less.

INVENTORIES OF MEDICAL CARE

The public opinion survey comprised one of the six key phases of the fact-finding survey that was conducted by the study committee in Charlotte and Mecklenburg County. The other five phases included individual inventories of physicians, nurses, hospitals, dentists, and public health services, covering personnel and facility resources.

Of the 205 physicians engaged in active private practice in Mecklenburg County, 152 answered part or all of the inventory questionnaire on physician personnel. All percentages given are of those expressing an opinion. The replies show that the vast majority of physicians, or 97%, usually answer night calls from their own patients when the illness or injury comes within their field of practice. But the number of physicians is somewhat less, 80%, who will take night calls from new patients.

The next question asked was, "Considering 100% as your desired optimal load of medical practice, with due regard to adequate attention to the patient on the one hand, and to your own time and health—but not money—on the other hand, during the past six months what percentage of this load have you averaged?" (An overworked doctor might answer 125%; a newly established doctor 30%.) At least 32 out of the 152 physicians replying would like to, and were able to, take on a quarter more or even double the amount of work that they were doing. They were mostly the younger, less well known men. The 60% of the public who thought there was a shortage of doctors in Mecklenburg County and the 34% who thought there was a shortage of surgeons are not aware apparently that a number of younger doctors have entered practice in their county who could take care of considerably more patients.

The great increase of physicians in Mecklenburg County following the end of World War II was evidenced by the 40% who replied that they had practiced in Charlotte five years or less at the time of the 1951 inventory. Another 10% have been in practice less than 10 years.

Slightly under 40% (38.1) were engaged in either general practice or internal medicine; the division was about half and half. The remaining 62% practiced in the fields of general surgery, obstetrics and gynecology, pediatrics, urology, ophthalmology, orthopedics, ear, eye, nose and throat, radiology, dermatology, neurosurgery, pathology, neurology-psychiatry, and proctology in that descending order from 9% to 1%. Judging from the fields of practice reported, Mecklenburg County is "short" on general practititioners and "long" on board-certified specialists. Many specialists do serve, even so, as "family" or "personal" physicians.

That the great majority of the physicians in Mecklenburg County were willing to take care of charity patients was evidenced by the fact that 96% accept and treat patients unable to pay, and another 3% do so occasionally.

Physicians were asked: "Excluding pure charity, what percentage of your 1950 accounts did you collect?" In over half of the cases, the answers were an estimated amount rather than a recorded one. Eighteen physicians collected over 90% of their accounts. Ninety-two physicians collected 75 to 90% of their acocunts. Twenty-five physicians collected 48 to 74% of their accounts.

The next question sought to determine the percentage of a doctor's patients coming from outside the county. Forty-six physicians reported 5 to 8%. Thirty-four physicians reported 10 to 25%. Thirty-two physicians reported 26 to 50%. Twenty-three physicians reported over 50%. It is to be expected in a medical center that a significant amount of time would be spent by the medical profession in the care of out-of-county patients.

The inventory of physicians' data indicates that there is no drastic shortage of physicians in the community. The data reveals also that a great majority of the doctors in Mecklenburg County do their best to meet the demands made upon them. The most acute need indicated by the inventory is for additional general practitioners, particularly more Negro physicians. This, the physician's "side of the story," makes an interesting comparison with comments by the public.

ALLIED INVENTORY FINDINGS

Lack of space and consideration for length rule out covering in detail the inventory findings for hospital, nurse, public health, and dental personnel and facilities in Mecklenburg County.

The total of 1,032 general hospital beds and 161 bassinets available in Charlotte on March 1, 1952, exceeds the minimum of 4.5 beds per 1,000 population that the U. S. Public Health Service says a "base area," such as Charlotte, should have. Three general hospitals for white persons reported 82 additional beds were under construction in 1952. The rate of bed occupancy in these three hospitals was 87%. (The United States average was 74% that year.)

The 394 graduate active nurses (nonfederal) per 100,000 population counted in the community study was more than double the national average of 188 in 1949. Nevertheless it is difficult in the city and county to obtain a private duty nurse on short notice, particularly for night duty. It is estimated that there are at least 100 additional registered nurses in the county who are inactive.

The department of health in Charlotte ranked second in expenditures from local sources, sixth in expenditures from all sources, and fourth in dollars and cents per capita in all public and private agencies. Its $3.14 per capita expenditure is considered very good. The public health department of Mecklenburg County had a per capita expenditure of $1.46 in 1950. Its 1950 budget was $92,270. This contrasts with a $421,362 budget for the Charlotte public health department. From the over-all viewpoint, merger of the health departments of the city and of the county is desirable and should be accomplished without lowering any of the standards now maintained in the city.

A dentist-population ratio of 41 nonfederal dentists per 100,000 population in Mecklenburg County does not equal the national average of 53 dentists per 100,000 population in 1950. Five of the 49 answering dentists, however, are

doing only 30 to 70% of the amount of dental practice that they would like to do, and another 15 are doing only 75 to 95% of the optimal load they desire. The inventory showed that local dentists spend much less time caring for out-of-the-county patients than do the physicians.

THE STUDY COMMITTEE'S RECOMMENDATIONS

Based on the public opinion survey and inventory findings, the Study Committee of the Mecklenburg County Medical Society formulated these recommendations to the profession:

A. In the Field of Professional Service:

1. Be sure your fees are "fair." In order to avoid misunderstandings about financial matters, encourage discussion of major charges in advance (*a*) by displaying the A. M. A. plaque entitled "To All My Patients" in your waiting room or consultation room, and (*b*) by bringing up the subject yourself or, if you prefer, suggest that the patient discuss it with your (properly trained) secretary.

2. Improve the servicing of house calls, especially at night, both personally and by participation in the emergency and information service plan. When called by a patient whose complaint does not properly require your own services, contact a colleague yourself and arrange service.

3. Encourage more specialists to serve as family or personal physicians, at least to some extent (for example, as explained in point 2).

4. Improve practice procedures, such as (*a*) when too busy to take a new patient, refer him to a colleague, perhaps to a younger man who may not be too busy; (*b*) render itemized bills; and (*c*) maintain adequate office space and adequate well-trained personnel, so that you may render good service with a minimum of waiting time.

5. Encourage more physicians and dentists, particularly general practitioners, to come to the community. Negro members of these two professions are especially needed.

B. In the Field of Public Health:

1. Direct added efforts toward reducing the neonatal mortality.

2. Provide additional clinics for Negro children.

3. Promote a satisfactory merger of the city and county health departments.

C. In the Field of Information for the Public:

1. Encourage everyone to have a "family doctor."

2. Bring before the public, through various mediums, the facts about (*a*) actual operating expenses and overhead costs of physicians and dentists; (*b*) the cost of training physicians and dentists, and what is being done in our own state to produce more; (*c*) the relatively small increase in professional fees as compared with the increase in prices of food, clothing, and other basic requirements during the past 12 years; (*d*) why hospital costs are what they are; and (*e*) the advantages of a combined city and county health department.

CONCLUSION

Because most of the members of the study committee are engaged in private practice, this work had to be done in what "spare time" was available, which meant evenings not devoted to other medical meetings and Sunday afternoons. As a result, almost two years were required to obtain, assemble, tabulate, and analyze the data. As the work of the committee progressed, the findings were presented first to the county medical and dental societies and then released in unaltered form, with their permission, to the local newspapers. By demonstrating our desire to bring to light any deficiencies in our field of service to the citizens of this community, we believe we have enhanced our relations with them. We believe that deficiencies such as these, once known, can best be remedied by efforts initiated at the local and county level. We now have a sound basis on which to formulate improvements that should be of value to the patients and to all professional personnel engaged in serving the medical needs of the community.

403 N. Tryon St.

STATEMENT BEFORE HOUSE COMMITTEE ON INCOME TAX DEDUCTION OF MEDICAL EXPENSES

Gentlemen: I am Dr. David B. Allman of Atlantic City, N. J., where I am engaged in the active practice of medicine. I am a member of the Board of Trustees of the American Medical Association and I am appearing here today (June 17, 1953) as a representative of that Association relative to the deduction of medical expenses for income tax purposes.

The Committee on Legislation of the American Medical Association has considered a number of bills introduced during the 81st, 82nd and 83rd Congresses which are designed, in general, to authorize the deduction of all, or a larger percentage of medical expenses, from gross income for income tax purposes. The effect of this legislation would be to reduce or remove the limitation on such deductions imposed by existing law. Certain of these bills would also redefine the term "medical expenses" to include amounts paid as premiums for prepayment health insurance.

The principle involved in all of these measures has been actively approved by the Committee on Legislation and by the Board of Trustees of the American Medical Association. Although no attempt has been made to work out the details of the formula to be applied, we are of the opinion that a greater measure of relief should be provided in this way for those individuals who have suffered from the financial burden resulting from the expense of a serious, long-term illness.

Although, as previously stated, the Association is on record as supporting legislation of this type, it might be well to discuss certain misconceptions concerning the present cost of medical care. Taken as a whole, medical costs are not out of line with other normal living expenses. Statistics presented by the United States Department of Labor for the third quarter of 1952 reveal that living costs have increased 90.8% since 1935-1939, while medical costs have increased only 65.5% in the same period.

In addition, it should be noted that recent surveys indicate that only 3% of American families have medical bills over $200 and that 80% have no medical debts of any kind. Despite this fact, it is realized that a serious long-term illness can be a financial catastrophy to almost any family. Thus for some time, several insurance companies have been experimenting in a relatively new form of insurance called, among other titles, "medical disaster" or "catastrophic" coverage. A few of the agencies established by medical associations are also underwriting this newer version of protection. Its purpose is to provide sound protection in those instances requiring long-term or high-cost treatment. These ventures are being undertaken with the knowledge and full support of the medical profession.

The provisions of the bills pending before this Committee which are designed to permit deductions from gross income for the cost of prepayment health insurance should act as an inducement for people to join medical and hospitalization plans. Although the growth of voluntary health insurance is unparalleled in comparison with other advances recorded in the recent history of insurance, there are still segments of the population that are not covered. Despite the fact that 90,000,000 Americans have some form of protection, both physicians and underwriters are reviewing the basic standards of insurance to seek ways and means of improving this coverage.

We believe that the enactment of legislation of this type will further encourage the improvement of existing plans, will extend coverage, and will help to eliminate or reduce the financial burdens which do exist as a result of illness. It will also encourage people to look after their own health rather than turn to the government for assistance. We are sincerely convinced that our present nongovernmental system of medicine not only provides the best care but that it is also the most economical. We are therefore in accord with any legislation designed to help preserve that system.

STATEMENT BEFORE HOUSE COMMITTEE ON REORGANIZATION OF DEPARTMENT OF DEFENSE

Gentlemen: I am Dr. David B. Allman of Atlantic City, N. J., where I am engaged in the active practice of medicine. I am a member of the Board of Trustees of the American Medical Association and I am appearing here today (June 18, 1953) as a representative of that Association relative to Reorganization Plan No. 6, 1953.

Although all of the provisions of the proposed Plan to reorganize the Department of Defense are of interest and concern to physicians as individual citizens, the interest of the American Medical Association is confined to Section 3 of the Plan.

This section would authorize the appointment of six additional Assistant Secretaries of Defense from civilian life by the President by and with the advice and consent of the Senate. Although the specific duties of these Assistant Secretaries are not specified in the Reorganization Plan, it is assumed that the assignments suggested by the report of the Rockefeller Committee on the Department of Defense organization dated April 11, 1953, would be favorably considered.

As you are well aware, it is the recommendation of the Rockefeller Committee that one of the proposed Assistant Secretaries be placed in charge of health and medical affairs with the responsibility for "maintaining high health standards among the personnel of the Armed Forces and for providing and managing hospitals and other medical installations at the smallest possible cost in dollars and professional personnel."

On Feb. 7, 1953, the Board of Trustees of the American Medical Association approved a recommendation of the Council on National Emergency Medical Service that a position as Assistant Secretary of Defense for Health and Medical Affairs be created by law. The Association believes that creation of such a position would insure proper correlation of military and civilian medicine, especially in the matter of apportionment of essential, highly trained health personnel.

Although it is impossible to date the inception of the interest of the American Medical Association in military medical affairs, I should like to call the attention of the Committee to the activities of the Association in this regard since the enactment of special draft legislation designed to procure physicians for the Armed Forces.

In August, 1950, and again last month the medical profession, after careful and thoughtful consideration, supported the need for special draft legislation, notwithstanding its discriminatory character. The Association, in its discussions with the Department of Defense and in its testimony before the various committees of the Congress, has clearly stated its desire to terminate such legislation at the earliest possible time. We have consistently recommended strongly that physicians and dentists called to active duty in the armed forces under this law be used efficiently and, except in unusual circumstances, for care of military patients rather than nonmilitary personnel.

However, since the original enactment of this legislation in 1950, nonmilitary medical activities have increased. We have been advised by representatives of the Department of Defense that compulsory legislation of this type will be necessary for five additional years or, until 1958. It is understandable, therefore, that the medical profession is seriously concerned and desirous of discovering alternative methods for meeting the requirements of the Armed Forces for health personnel.

The existence of this law, plus the continuing need for civilian medical participation in military planning and operations as they relate to medical and health services and to the assignment and utilization of medical and allied health personnel, we believe, necessitates competent high-level civilian direction within the Department of Defense. We are happy to note that in this regard the message of the President of the United States transmitting Reorganization Plan No. 6 to the Congress states: "There must be a clear and unchallenged civilian responsibility in the Defense Establishment."

It is our belief that the incumbent of the position as Assistant Secretary for Health and Medical Affairs should advise the Secretary of Defense concerning the development of policies, procedures and programs dealing with the coordination of the medical and hospital services of the Armed Forces and the mobilization and utilization of health personnel.

STATEMENT BEFORE HOUSE COMMITTEE ON INCOME TAX DEDUCTION OF EDUCATIONAL EXPENSES

Gentlemen: I am Dr. Walter B. Martin of Norfolk, Va., where I am engaged in the active practice of medicine. I am President-Elect and a member of the Board of Trustees of the American Medical Association and I am appearing today (June 18, 1953) as a representative of that Association relative to the deduction of college and educational expenses for income tax purposes.

The American Medical Association has not taken any position with respect to the deduction of all college and educational expenses for income tax purposes. However, the Association is vitally interested in the deduction of postgraduate educational expenses. Although the present tax laws permit such deductions for ordinary and necessary expenses in a trade or business, there is no express provision permitting professional persons to deduct the cost of securing additional education.

In connection with postgraduate medical education, your Committee may be interested in the fact that there is a total of 784 postgraduate courses available at this time. Of this number 418 are offered on a full-time basis and 366 on a part-time schedule. These courses, which are available in 37 states, the District of Columbia and Puerto Rico, cover 34 major areas in the field of clinical medicine and 9 basic science subjects.

A total of 134 agencies offer postgraduate medical training including 43 medical schools, 35 special medical societies, 18 hospitals, 12 academies of general practice, 11 state medical societies, 6 graduate schools of medicine and 3 agencies representing boards of health, schools of public health and government departments respectively.

These courses are designed to be of assistance to physicians in general practice as well as to specialists in increasing their medical proficiency as well as to prepare them for specialty board certificates.

For a considerable number of years the House of Delegates and the Board of Trustees of the Association have expressed concern over a ruling by the Commissioner of Internal Revenue holding that expenses incurred by a physician in pursuing postgraduate medical education are personal in nature and therefore not deductible for federal income tax purposes. It has been extremely difficult to understand the validity of such a ruling because of the fact that physicians have been permitted to deduct the costs of attending medical meetings, of subscriptions to scientific publications and of dues paid to medical societies.

Some time ago the Board of Trustees authorized the employment of a Special Tax Counsel to pursue this matter on behalf of the Association. In an unsuccessful effort to obtain a new ruling from the Bureau of Internal Revenue, it was learned that there was pending before the United States Tax Court a case in which a lawyer had been denied the right to deduct expenses incurred by him in attending postgraduate courses on taxes. In view of the fact that the case involved was quite similar to the one in which the medical profession was interested in, the American Medical Association filed a brief as amicus curiae. The tax held against the taxpayer and an appeal was made to the United States Court of Appeals. On April 14 the United States Court of Appeals reversed the decision of the United States Tax Court holding, in effect, that expenses incurred by the attorney in taking a postgraduate course were deductible for income tax purposes.

While it is the belief of the American Medical Association that this decision probably applies to the practicing physician who attends postgraduate courses which are similarly designed to refresh his medical knowledge and to keep him informed regarding recent medical developments, it is by no means clear that the Court's decision covers attendance at postgraduate courses which are designed to advance the physician into a new area of his profession. For example, there is considerable doubt whether a general practitioner may deduct his expenses in attending a postgraduate course in order to specialize in surgery.

Also, it is not clear just how far the Bureau of Internal Revenue or the courts will follow this decision. If it is interpreted liberally all business and professional men will be entitled to deduct expenses incurred in attending refresher courses providing that there is a demonstrable tie-in with their official duties. It appears more likely, however, from the wording of the decision, that a deduction would be disallowed in cases in which the taxpayer fails to show that he was bound, either contractually or morally, to keep abreast of changes in his particular field, and that attendance at an institute or refresher course was the proper way to do it.

In view of these areas of doubt, it is the belief of the American Medical Association that the issue should be settled by new legislation rather than be left to administrative interpretation or judicial decision. We would strongly urge, therefore, that your committee give favorable consideration to an amendment to the existing law authorizing the deduction of postgraduate educational expenses for income tax purposes.

FEDERAL MEDICAL LEGISLATION

Withholding Health Insurance Premium for Federal Employees

Senator Carlson (R., Kans.) in S. 2191 would authorize the withholding from federal payrolls of subscription charges for voluntary prepayment hospital and medical care insurance programs, at the request of the employee. The withheld money would be paid by the federal agency to the respective voluntary prepayment plans selected by the employee. This measure is similar to H. R. 1590 by Congressman Miller of California, previously reported. However, the Miller bill would cover accident and life insurance as well as health and hospitalization insurance. This measure was referred to the Post Office and Civil Service Committee.

Care of Veterans in State Veterans' Homes

At the request of the American Legion, Congresswoman Rogers (R., Mass.) would amend the present law to authorize, in H. R. 5892, a federal contribution of $700 per annum per veteran cared for in a state or territorial veterans' home, but the federal contribution could not exceed half of the total cost per veteran. Eligible veterans are those "disabled by age, disease, or otherwise, and by reason of such disability incapable of earning a living, provided such disability was not incurred in service against the United States." The present law authorizes a federal contribution of $500 annually until 1956 and $300 thereafter. In the fiscal year ending June 30, 1952, the federal contribution under this program amounted to $3,892,135.15. The bill was referred to the Veterans' Affairs Committee.

Medical and Hospital Care for Disabled Retired Veterans

Congresswoman Rogers (R., Mass.) proposes in H. R. 5893 that "any person retired from active service in the Armed Forces of the United States, who is in need of medical or hospital care for an injury, disability, or disease incurred or aggravated in line of duty in such service and who would be eligible to receive disability compensation from the Veterans Administration if he were not receiving retired or retirement pay shall be entitled to receive such care from the Veterans Administration . . . subject to the same limitations as such care is furnished to veterans who are in receipt of disability compensation from the Veterans Administration." Under the present law, a veteran receiving a disability pension from the Veterans Administration is entitled to hospitalization for a service-connected condition. However, a veteran receiving disability retirement pay from one of the armed forces in certain circumstances would have to renounce his military pay during the period of treatment and qualify for a VA pension. The proposed bill would amend the law to authorize hospitalization for a service-connected condition without requiring the veteran to have one form of compensation replaced by another. This measure was introduced at the request of the American Legion to carry out a mandate of its last convention. This measure was referred to the Veterans' Affairs Committee.

Total Disability Insurance Benefits

Congressman Radwan (R., N. Y.) in H. R. 5917 would amend the Social Security Act to provide disability insurance benefits for totally disabled persons. Disability is defined as: "(A) inability to engage in any substantially gainful activity by reason of any medically determinable physical or mental impairment, or (B) blindness." Who shall determine disability is not specified. The amendment was referred to the Ways and Means Committee.

Problems of the Aged

Congressman Campbell (D., Fla.) in H. R. 309 would create a select committee to be composed of seven members of the House of Representatives to investigate (*a*) the status of older persons, (*b*) "the most effective utilization of our older population group," and (*c*) the basic problems in the fields of employment, health, education and community services of our older population group. The resolution is identical with H. R. 13 (Bolling), previously reported, and four other resolutions. It was referred to the Rules Committee.

STATE MEDICAL LEGISLATION

Connecticut

Bills Enacted.—H. 993, has become Special Act No. 239 of the Acts of 1953. It directs the governor to appoint a commission to make a study of **the potentials of the aging residents of the state,** including a survey of the employment and security problems of persons who have attained the age of 65. S. 722, has become public act no. 244 of the acts of 1953. It requires **physicians to report** to the state department of health the name and address of each person known to him to be subject to recurrent attacks of **epilepsy** or to recurrent periods of unconsciousness uncontrolled by medical treatment.

Florida

Bills Enacted.—H. 535, became law without approval, June 15, 1953. It authorizes the **state board of osteopathic medical examiners** to pass upon the standing and reputability of osteopathic schools and colleges and osteopathic hospitals. H. 557, became law without approval, May 21, 1953. It provides that states attorneys or county solicitors may, in their discretion, **have autopsies performed upon dead bodies** found within the county, either before interment or after, whenever in their opinions such autopsies are necessary in order to ascertain whether death resulted from a criminal act or by the result of criminal negligence. H. 1680, became law without approval, June 15, 1953. It authorizes the county commissioners in certain counties in the state to include in the annual budget an item for a **full-time local health unit** and to contribute and pay from the general fund to the state treasury to the account of the state board of health a sum of money for the maintenance of a full-time local health unit. S. 351, was approved June 12, 1953. It provides for the **licensing and regulation of nursing homes.**

New Jersey

Bill Introduced.—A. 664, to amend the **medical practice act,** proposes that any veteran who shall be more than 30 years of age, of good moral character, and a citizen of the United States and a resident of this state, and who has or shall have completed a four-year-course of study in a public high school, a four-year premedical course of study in a premedical college, a four-year course of study in and a degree of doctor of medicine from a medical college, two years of service as an intern or resident physician in a hospital licensed in the state, and who has successfully passed an examination given by a state board in another state in the subjects of anatomy, physiology, pathology, chemistry, and bacteriology, and who is licensed to practice medicine and surgery in such state, shall be entitled to a license to practice medicine and surgery in New Jersey.

Bill Enacted.—A. 137, has become ch. 190 of the laws of 1953. It requires **every physician to report** to the office of the superintendent of state police within twenty-four hours after determining that any person is suffering from the effect of the use of a narcotic drug taken for purposes other than the treatment of sickness or injury as prescribed or administered by a person duly authorized by law to treat sick and injured human beings.

Vermont

Bill Enacted.—S. 10, was approved May 26, 1953. It amends the law relating to medical examiners by providing that the state pathologists may appoint 25 **medical examiners** who shall be licensed doctors of medicine or osteopathy.

The summary of federal legislation was prepared by the Washington Office of the American Medical Association and the summary of state legislation by the Bureau of Legal Medicine and Legislation.

MEDICAL NEWS

ARKANSAS

State Medical Election.—At the annual meeting in Little Rock the Arkansas Medical Society elected Dr. Richard C. Dickinson, Horatio, president; Dr. William R. Brooksher, Fort Smith, president-elect; Drs. John H. Wilson, Magnolia, Thomas Wilson, Wynn, and Johnnie P. Price, Monticello, vice-presidents; Dr. Daniel H. Autry, Little Rock, treasurer; and Dr. John J. Monfort, Batesville, secretary.

University News.—The University of Arkansas School of Medicine, Little Rock, has received a gift of $1,000 from Dr. Louis Friedman of Birmingham, Ala., to promote alumni activities and public relations.——O. Boyd Houchin, Ph.D., Iowa State College, has been appointed assistant professor of neurology at the University of Arkansas School of Medicine, Little Rock. Dr. Houchin will devote his time to the study of the biochemistry of the brain, a project now in operation in the department of neurology under the sponsorship of the United Cerebral Palsy Associations, Inc.

CALIFORNIA

Joseph McCarthy Prize Awarded.—At the recent meeting of the Western section of the American Urological Association, in San Francisco, the Joseph F. McCarthy prize essay award of $200 was given to Drs. Joseph J. Kaufman, Beverly Hills, Milton Rosenthal, Culver City, and Willard E. Goodwin, Los Angeles, for their paper "Methods of Diagnosis of Carcinoma of the Prostate: A Comparison of Clinical Impression, Papanicolaou Stains, Needle Biopsy, Transurethral Biopsy and Open Perineal Biopsy." The study emanated from the University of California at Los Angeles School of Medicine and the VA Center, Los Angeles.

Japanese Honor Colonel Hunter.—Residents of Nagatoishi-cho, Japan, have erected a monument to Col. George W. Hunter, Ph.D., San Francisco, who from 1947 to 1949 supervised periodic spraying of irrigation ditches in their city, which were breeding grounds for disease-bearing snails. Incidence of schistosomiasis is said to have been reduced by more than 98%. The monument is a life-sized bronze bust of Dr. Hunter, resting on a cairn of native rock. The inscription, chiseled in Japanese, reads in part: "His sacrificial work and guidance over the two years were greatly appreciated by the population. It is our sincere wish to erect this bronze statue for Doctor Hunter in order to praise and remember forever his great work."

COLORADO

Awards in Recognition.—At the annual banquet of the University of Colorado Medical Alumni Association, Awards in Recognition were made to the following graduates of the University of Colorado, or of the Gross Medical College or the University of Denver College of Medicine, which were absorbed by it: Drs. Edward Delehanty Sr., Charles S. Elder, Aubrey H. Williams, George R. Warner, Rudolph W. Arndt, Archibald D. Attwood, Robert W. Fraser, John M. Barney, Wilson C. Birkenmayer, Cuthbert Powell, Charles A. Bundsen, Walter W. King, Denver; Dr. Angus Taylor, Pueblo; Dr. Walter S. Chapman, Walsenburg; Drs. Frederick W. Lockwood and Arthur F. Williams, Fort Morgan; Dr. John H. Larson, Wray; Dr. Edward W. Lazell, Santa Barbara, Calif.; Dr. Tobias Espinosa, Espanola, N. Mex.; and Dr. Ella A. Mead, Greeley. All persons who received the award have been in practice 50 or more years.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education and public health. Programs should be received at least three weeks before the date of meeting.

CONNECTICUT

Industrial Institute at Yale Center of Alcohol Studies.—To meet the demand for specialized training of key personnel in the establishment of programs of education and rehabilitation of problem drinkers in business and industry, the Yale Center of Alcohol Studies, New Haven, will conduct a training session at Yale University July 27-31. The session will acquaint selected representatives of business and industry with the nature of problem drinking in industry; with policies of treatment, retirement, and separation; with procedures and resources for treatment; and with programs of education and prevention. Among the lecturers will be Drs. S. Charles Franco, Brooklyn, associate medical director, Consolidated Edison Company of New York; Giorgio Lolli, research associate, applied physiology, Yale University, and medical director of the Yale Plan Clinic and the Connecticut Commission on Alcoholism; Robert C. Page, New York, general medical director, Standard Oil Company of New Jersey; and Arnold Z. Pfeffer, assistant clinical professor of psychiatry, New York University College of Medicine and physician-in-charge, Consultation Clinic for Alcoholism, University Hospital, New York. The first two days of the session will be devoted to lectures and discussions covering the physiological, psychological, and sociologic aspects of the problem. Requests for additional information and applications for admission should be addressed to Yale Center of Alcohol Studies, Industrial Institute, 52 Hillhouse Ave., Yale Station, New Haven.

DISTRICT OF COLUMBIA

Dr. Forster Named Dean.—Dr. Francis M. Forster, head of the department of neurology, has been named head of the Georgetown University School of Medicine to succeed the Reverend Paul A. McNally, S.J., regent and dean of the school of medicine, who has been forced to relinquish his position because of ill health. The Reverend McNally will become dean emeritus and director of the Georgetown Medical Center. Dr. Forster was previously affiliated with Jefferson Medical College, Philadelphia, Harvard Medical School, Boston, Boston University School of Medicine, and Yale University School of Medicine, New Haven, Conn. He has served at Good Samaritan Hospital in Cincinnati, Boston City Hospital, and the Pennsylvania Hospital in Philadelphia. He is the former secretary and present chairman of the A. M. A. Section on Nervous and Mental Diseases. He will retain his present post as professor of neurology and head of the department.

ILLINOIS

Personal.—Dr. George H. Vernon, for many years director of the Palmer Sanatorium in Springfield, has accepted appointment as director of the Madison County Sanitarium, Edwardsville.

Welfare Advisers Named.—Dr. Otto L. Bettag, Illinois state director of public welfare, has appointed as consultant in psychiatry Dr. Roy R. Grinker, clinical professor of psychiatry at the University of Illinois College of Medicine, Chicago, and director of the Institute for Psychosomatic and Psychiatric Research and Training of Michael Reese Hospital, and as consultant in research Dr. Ralph W. Gerard, professor of neurophysiology and physiology, University of Illinois College of Medicine.

Society News.—At the annual meeting of the Illinois Chapter of the American College of Chest Physicians, Dr. Abel Froman, Chicago, was elected president, Dr. Clifton F. Hall, Springfield, vice-president, and Dr. Albert H. Andrews Jr., Chicago, secretary.——The Scientific Service Committee of the Illinois State Medical Society is revising the list of speak-

ers available to county medical societies. All physicians wishing to be included are urged to send in their names, a list of subjects for which they would be available, and their affiliations with medical school teaching staffs and hospital staffs. Mention should also be made of the type of slides used in talks and titles of movies if available. Write to Dr. Louis R. Limarzi, Chairman of the Scientific Service Committee, Illinois State Medical Society, Rm. 801, 185 N. Wabash Ave., Chicago 1.

Chicago

Residence Hall at Cook County Hospital.—The Dr. Karl A. Meyer Hall, a 15 story residence for interns and resident physicians at Cook County Hospital, was recently dedicated. The new 3 million dollar building, at 720 S. Wolcott Ave., is connected to the hospital by a tunnel. It will house 297

Karl A. Meyer Hall

persons. There are 283 single rooms for interns, 12 two room and 5 five room apartments for staff, a cafeteria, gymnasium, handball courts, game room, and snack bar. The library has been named in honor of Dr. Frederick Tice, who has served the hospital for many years.

Personal.—Dr. Donald G. Anderson, Chicago, Secretary of the A. M. A. Council on Medical Education and Hospitals, delivered an address "The Rebellion Against the Teaching of Scientific Medicine" at the recent commencement exercises of Boston University School of Medicine.——Dr. William S. Kroger, assistant professor of gynecology, Chicago Medical School, gave a lecture "The Use of Hypnosis in Child Birth," with color and sound film, at Sinai Hospital, Baltimore, June 1; to the obstetric department of Johns Hopkins University School of Medicine, Baltimore, June 2; and at Mount Sinai Hospital, New York, June 5.——Dr. George Halperin, associate editor of THE JOURNAL, returned recently from a five week trip to France, Italy, and Israel, where he delivered a lecture on medical journalism before the faculty of the medical school of the Hebrew University of Jerusalem and the medical profession.

MARYLAND

Society News.—The Radiologic Section of the Baltimore City Medical Society recently elected Dr. David N. Gould, Johns Hopkins Hospital, Baltimore, chairman, and Dr. H. Leonard Warres, 2337 Eutaw Place, Baltimore 17, secretary.——At the initial meeting of the Maryland Radiological Society, the following officers were elected for the coming year: chairman, Dr. Richard B. Hanchett, Baltimore, vice-chairman, Dr. Edgar T. Campbell, Hagerstown, and secretary-treasurer, Dr. H. Leonard Warres, Baltimore.

Dean of Medical Faculty.—Philip Bard, Ph.D., professor of physiology at the Johns Hopkins University School of Medicine, Baltimore, has been appointed dean of the medical faculty to succeed Dr. Alan M. Chesney, who has retired after nearly 25 years as dean of the school. In addition to serving as dean, Dr. Bard will continue in his present position in the department of physiology. He is the author of numerous scientific papers based on his research in physiology and medicine. During World War II, Dr. Bard served as special consultant to the government in the Office of Scientific Research and Development and on committees of the National Research Council. He has served on the faculties of Harvard and Princeton and has been selected to deliver numerous memorial lectures. Dr. Chesney, who has been dean of the school of medicine since 1929, will continue his association with the Hopkins institutions in an emeritus capacity. He plans to devote his immediate future to the completion of the second volume of his chronicle "The Johns Hopkins Hospital and the Johns Hopkins University School of Medicine," the first volume of which was published in 1943. Dr. Chesney was one of the founders of the Maryland Society for Medical Research, composed of laymen and physicians, which battled the antivivisectionists to an overwhelming defeat at the polls in 1950, when the antivivisectionists took the fight before the public on a referendum question.

MASSACHUSETTS

Dr. George Shattuck Honored.—Dr. George C. Shattuck, clinical professor of tropical medicine, emeritus, Harvard Medical School, Boston, was recently honored for 30 years of service as chairman of the health council of the United Community Services of Metropolitan Boston. During a meeting at which Dr. Shattuck's retirement from the chairmanship was announced, the Health Council presented him with a citation which read in part: "The work which this organization has accomplished has been due in large part to your comprehension of public health work and your awareness of the needs of the community."

Dr. Schmidt Joins American Joint Distribution Committee.—Dr. William M. Schmidt, since 1949 associate professor of maternal and child health practice, Harvard University School of Public Health, Boston, has submitted his resignation and in September will return to his former work as medical adviser to the executive council of the American Joint Distribution Committee with headquarters in Paris. Dr. Schmidt, who was previously regional consultant to the U. S. Children's Bureau in Washington, D. C., in 1950 made a survey for the state department of maternal and child health in the U. S. zone of Germany. He attended the first meeting of WHO's Expert Panel on Maternity Care in Geneva, November, 1951. While at Harvard, he served also as associate physician of the Children's Medical Center Child Health Division.

MISSOURI

State Medical Election.—At the Kansas City session the Missouri State Medical Association installed Dr. E. Claude Bohrer, West Plains, as president and chose the following officers: Dr. Harold E. Petersen, St. Joseph, president-elect; Drs. Guy N. Magness, St. Louis, Frank R. Teachenor, Kansas City, and Thomas E. Ferrell, Springfield, vice-presidents; Dr. Carl F. Vohs, St. Louis, treasurer; and Dr. Edward R. Bohrer, Jefferson City, secretary.

NEW JERSEY

Cardiovascular Traineeship.—St. Michael's Hospital, Newark, announces the establishment of a full-time traineeship program in cardiovascular diseases, approved by the National Heart Institute. Information may be obtained from Dr. Nicholas A. Antonius, director of the department of cardiology.

Personal.—Dr. Frederick F. Yonkman, vice-president in charge of research for Ciba Pharmaceutical Products, Inc., Summit, has been elected to serve as a trustee of the Columbia University College of Pharmacy, New York. Dr. Yonkman is on the teaching staff of Columbia University College of Physicians and Surgeons.——Dr. Henry H. Kessler, Newark, was recently named "citizen of the year" by the New Jersey Society of Professional Engineers, at a dinner at the Hotel Essex House, Newark.——Dr. Harry B. Slocum was honored at a dinner celebrating his 50 years on the medical staff of Monmouth Memorial Hospital, Long Branch.——The staff of Overlook Hospital, Summit, recently honored the following physicians for their service to the hospital and community: Dr. John L. Meeker, former staff member, who has practiced for 50 years and is now a consultant in medicine; Dr. Arthur E. Tator, who was retiring from the active staff to become surgical consultant; Dr. Cedric C. Carpenter, who recently retired as president of the hospital medical staff; and Dr. John M. Atkinson, Madison, who succeeded him.

NEW YORK

Grant for Air Research.—Dean Harold C. Wiggers, Ph.D., of Albany Medical College, has announced that a $5,000 grant-in-aid has been given to the college by the Air Research and Development Command of the Air Force for studies on the effects of temperature extremes on body fluids and electrolytes. Gerald S. Kanter, Ph.D., who joined the medical college staff last year as instructor in physiology after doing research on the subject at the University of Rochester School of Medicine and Dentistry, will carry out the studies.

Art Contest.—The Academy of General Practice Art Convention, which will hold its scientific exhibit at the Hotel Statler, New York, Oct. 28-30, invites physicians of New York State to submit entries. A war bond prize will be awarded to the physician who best interprets in an oil painting the theme "Medicine Today." Originality and oil technique will be among the features considered. Entries in other fields, such as photography, sculpturing, and hobby work, may also be submitted. Dr. F. Donald Napolitani, 2281 University Ave., New York, has been reappointed chairman of the convention.

New York City

Dr. McDonald Appointed Dean at Lebanon.—Dr. Joseph J. McDonald, visiting surgeon and director of surgical services, Francis Delafield Hospital, has been appointed dean of the Medical School of the American University of Beirut, Lebanon, to succeed Dr. Norman B. Nelson who was named dean of the State University of Iowa College of Medicine in Iowa City. Dr. McDonald, who served at the American University of Beirut as associate professor of surgery and chairman of the department from 1946 to 1950, was subsequently affiliated with Columbia University College of Physicians and Surgeons and Presbyterian Hospital.

Dr. Gasser Retires as Rockefeller Director.—Dr. Herbert S. Gasser, director of the Rockefeller Institute for Medical Research, recently reached the retirement age after more than 17 years of service. Dr. Gasser, who with Joseph Erlanger in 1944 received the Nobel Prize for discoveries concerning the differentiated functions of nerve fibers, joined the institute in 1935, succeeding its first director, the late Dr. Simon Flexner. He had previously been affiliated with (1) the University of Wisconsin Medical School, Madison, where as a student he served as instructor in physiology; (2) Washington University in St. Louis where he served as instructor in physiology and, after service in World War I, during which he did considerable research in traumatic shock and in chemical warfare, was named head of its department of pharmacology; and (3) Cornell University Medical College, New York, where he was professor of physiology and head of the physiological laboratories.

NORTH CAROLINA

Medical Town Hall.—Dr. George J. Baylin, program director, announces that Duke University School of Medicine, Durham, will present its second Medical Town Hall at 4 p. m. July 26, in the Physics Building auditorium. Topics will be skin diseases, including poison ivy, sunburn, poison oak, eczema, warts, acne, diaper rash, and other skin irritations. Speakers will be Dr. Susan C. Dees, associate professor of pediatrics, formerly a vice-president of the American College of Allergists, and Dr. J. Lamar Callaway, professor of dermatology, past president of the Southeastern Dermatological Association, and formerly vice-chairman of the Southern Medical Association. Five university faculty members will join Drs. Callaway and Dees as members of a panel to answer questions.

Health Center Dedicated at Chapel Hill.—The University of North Carolina at Chapel Hill recently dedicated as part of its new health center the North Carolina Memorial Hospital, the school of dentistry, the school of nursing, and the new four year expanded school of medicine. Dr. Henry T. Clark Jr., administrator of the Division of Health Affairs, presided at the program in Memorial Hall. The speaker was Dr. Joseph T. Wearn, dean and professor of medicine at Western Reserve University School of Medicine, Cleveland. Dr. W. Reece Berryhill, dean, presided at the school of medicine meeting at which a portrait of Dr. Hubert A. Royster, former dean of the medical school in Raleigh and dean emeritus of the university medical school, was presented. Dr. Royster, who is a past president of the North Carolina Medical Society, is now professor of surgery emeritus at Chapel Hill. Among the other speakers at the dedication services were Dr. David P. Barr, professor of medicine, Cornell University Medical College, New York, and Dr. Malcolm T. MacEachern, Chicago, director of professional relations, American Hospital Association.

SOUTH CAROLINA

State Medical Election.—At the annual meeting the South Carolina Medical Association installed Dr. Charles R. F. Baker, Sumter, as president, and chose as president-elect, Dr. Thomas R. Gaines, Anderson. Reelected were Dr. George D. Johnson, Spartanburg, vice-president; Dr. Robert Wilson Jr., Charleston, secretary; and Dr. J. Howard Stokes, Florence, treasurer. Mr. M. L. Meadors, Florence, was reappointed as executive secretary.

WEST VIRGINIA

Governor Appoints Licensing Board.—Dr. Oscar Bernard Biern, Huntington, who has served as secretary, vice-president, and president of the Cabell County Medical Society, and as chairman of the State Medical Association's committee on mental hygiene, has been named by Gov. William C. Marland as a member of the medical licensing board for a five year term to succeed Dr. Walter E. Vest, also of that city. Other physician-members of the board are Drs. Frank J. Holroyd, Princeton, George F. Evans, Clarksburg, Cecil B. Pride, Morgantown, William P. Bittinger, Summerlee, and Doff D. Daniel, Beckley. Dr. Newman H. Dyer, Charleston, state director of health, an ex officio member of the board, serves as its secretary.

WYOMING

Dr. McEnery Honored.—Dr. Douglas W. McEnery, cancer control officer and director of the division of communicable disease control, Wyoming Department of Public Health, was honored at a dinner given by the Wyoming division of the American Cancer Society, when an engraved medal from the American Cancer Society was presented to him.

GENERAL

Papers Invited for Cytology Meeting.—The first annual meeting of the Inter-Society Cytology Council will be held in Philadelphia, Nov. 19-20. Those interested in presenting papers pertaining to the cytological method for the diagnosis of cancer and related subjects are urged to send titles, together with an informative abstract of not more than 300 words, before Aug. 1 to the chairman of the program committee, Dr. Abraham E. Rakoff, Jefferson Medical College of Philadelphia, 1025 Walnut St., Philadelphia 3.

Psychiatric Endowment Fund.—The American Psychiatric Association (1785 Massachusetts Ave. N.W., Washington 6, D. C.) has established an endowment fund for the support of projects that will advance mental health. Contributions (which are tax exempt) will be used (1) to study the nature, causes, treatment, and prevention of mental disorders, (2) to raise standards of treatment and care for the mentally ill in hospitals, (3) to further psychiatric education and research, and (4) to make available psychiatric knowledge useful to other branches of medicine, other sciences, and to the public welfare.

Social Hygiene Awards.—At a social hygiene day luncheon in New York the American Social Hygiene Association recently awarded honorary life membership to Jacob A. Goldberg, Ph.D., director of the New York Tuberculosis and Health Association's social hygiene division, Dr. Charles D. Bowdoin, venereal disease control officer, Georgia Department of Public Health, Atlanta, and Dr. Gloyd G. Wetherill, director of health education, San Diego (Calif.) city schools. The association also bestowed on Bailey Barton Burritt, LL.D., the William Freeman Snow award for distinguished service to humanity.

Urology Award.—The American Urological Association offers an annual award of $1,000 (first prize $500, second prize $300, and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than 10 years and to men in training to become urologists. The first prize essay will appear on the program of the meeting of the American Urological Association at the Waldorf-Astoria, New York, May 31 to June 3, 1954. For full particulars, write the executive secretary, Mr. William P. Didusch, 1120 N. Charles St., Baltimore 1. Essays must be in his hands before Feb. 1, 1954.

Grant to Medical Social Workers.—A March of Dimes grant of $39,043 has been awarded by the National Foundation for Infantile Paralysis to the American Association of Medical Social Workers for improving standards of practice in medical social work and the educational programs of students being trained for this field. The foundation has appropriated $100,000 this year for the training of medical social workers. The scholarship program is administered directly by the national foundation with the assistance of a special scholarships committee that reviews the candidates' qualifications and recommends awards. Application for scholarships can be obtained from the National Foundation for Infantile Paralysis, Division of Professional Education, 120 Broadway, New York 5.

Research on Mental Illness.—The National Association for Mental Health has announced its intention to go into "large-scale" financing of research on mental illness. According to Mr. Robert M. Heininger, executive director, with the exception of a comprehensive research program on schizophrenia for which funds have been contributed during the past 16 years by the Thirty-Third Degree Scottish Rite, the organization has heretofore usually "been content to encourage research and to help initiate it through consultation with government bodies, universities, hospitals, and other research centers." The new plan contemplates the direct allocation of funds for research by means of grants and the creation of a commission for research on mental illness. Preliminary planning on the research program will get under way early in the fall.

Birth Rate Among College Graduates.—The Population Reference Bureau in Washington, D. C., has completed an eight year study of fertility rates of college graduates. It is said to show that the trend to have more children has been upward since 1936. Among the 1943 graduates, men averaged 1.63 children per graduate, and women, 1.30 children; among the 1936 graduates, fertility scores were 1.02 for men and 0.95 for women. The gain in the number of children per woman graduate of the class of 1943 over the alumnae of 1936 amounted to 36.8%. The study, conducted by Dr. Clarence J. Gamble and Mrs. Betty U. Kibbee, Milton, Mass., makes available data for individual colleges throughout the United States. Fertility scores of the 269 cooperating colleges are available on request to the Population Reference Bureau, Inc., 1507 M St., N.W., Washington 5, D. C.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories, and possessions in the weeks ended as indicated:

Area	July 4, 1953		July 5, 1952
	Paralytic Type	Total Cases Reported	Total
New England States			
Maine	..	3	2
New Hampshire	..	..	..
Vermont	..	1	1
Massachusetts	6	8	2
Rhode Island	..	1	..
Connecticut	1	6	2
Middle Atlantic States			
New York	10	50	24
New Jersey	..	4	2
Pennsylvania	..	3	4
East North Central States			
Ohio	7	23	45
Indiana	..	13	2
Illinois	9	21	4
Michigan	14	29	13
Wisconsin	..	2	3
West North Central States			
Minnesota	13	24	4
Iowa	5	16	27
Missouri	..	8	10
North Dakota	..	1	1
South Dakota	..	1	2
Nebraska	6	11	16
Kansas	..	10	17
South Atlantic States			
Delaware	..	3	..
Maryland	4	4	..
District of Columbia	..	2	..
Virginia	9	13	10
West Virginia	3	4	5
North Carolina	18	37	7
South Carolina	1	7	..
Georgia	..	20	11
Florida	2	19	10
East South Central States			
Kentucky	4	12	2
Tennessee	5	14	12
Alabama	11	22	17
Mississippi	..	16	26
West South Central States			
Arkansas	7	12	10
Louisiana	7	18	19
Oklahoma	16	41	26
Texas	17	81	186
Mountain States			
Montana	..	..	1
Idaho	..	1	1
Wyoming	..	..	..
Colorado	..	6	6
New Mexico	..	2	16
Arizona	..	1	7
Utah	..	4	1
Nevada	..	..	..
Pacific States			
Washington	..	6	14
Oregon	1	2	9
California	29	43	43
Territories and Possessions			
Alaska	..	..	..
Hawaii	..	..	18
Puerto Rico	..	..	..
Total	165	625	638

FOREIGN

British Occupational Hygiene Society.—This society was inaugurated at the London School of Hygiene and Tropical Medicine on April 27. In addition to physicians the founder members include engineers, chemists, and physicists. The first president of the society is Dr. T. Bedford, director of the Environmental Hygiene Research Unit of the Medical Research Council at the London School of Hygiene and Tropical Medicine.

Meeting on Logopedics.—The convention of the International Association of Logopedics and Phoniatrics will be held Sept. 1-5 at Zurich, Switzerland. Official reports will be given on "Congenital Language Disorders," "Physiology of the Voice," and "Electroacoustic Analysis and the Physiological and Esthetic Problems of the Voice." Requests for information should be sent to the Organizatory Committee, Piazza S. Ambrogio 9, Milano, Italy.

Angiologists to Meet in Lisbon.—The International Society of Angiology will hold a congress in Lisbon, Portugal, Sept. 18-20, under the presidency of Dr. Emile F. Holman, San Francisco. At a joint session with the International Society of Surgery, Friday, a symposium on aneurysms will be presented. Saturday there will be a symposium on mitral valvular surgery, and on Sunday an angiology forum. Information may be obtained from Dr. Henry Haimovici, Secretary General, 105 E. 90th St., New York 28.

Microbiologists Meet in Rome.—The International Congress for Microbiology will convene in Rome, Italy, Sept. 6-12 at the Città Universitaria. The following symposiums are planned: bacterial cytology; microbial metabolism; nutrition and growth factors; growth inhibitors and chemotherapy; morphology, biology, and systematics of the actinomycetales; and host-virus interactions. Communications should be addressed to the Segreteria del Congresso, Instituto di Igiene, G. Sanarelli, Città Universitaria, Rome, Italy.

India Speeds Birth Control Program.—Because government officials believe that the threat of overpopulation is too critical for further delay, the $1,300,000 birth control program, which was incorporated into India's master five year plan, adopted two years ago, is being put into operation ahead of schedule. T. Lakshmi Narayana, deputy director general of health services in charge of family planning, stated that the program was expected to be in full operation by the end of the year. India's population, estimated at 365 million persons, increased 42 million between 1941 and 1951.

Congress on Medical Librarianship.—The first International Congress on Medical Librarianship will be held in London July 20-25 in the anatomy and physiology lecture theaters, University College, Gower Street, with the inaugural session in Beveridge Hall, Senate House, University of London, Malet Street. Tuesday afternoon a symposium on the role of medical libraries in the world today, which will be continued on Wednesday morning, will be followed by the opening of the Armed Forces Medical Library Exhibition at Wellcome Research Institution, 183 Euston Road, N.W.1 (4 p. m.). Thursday morning there will be two simultaneous sessions on medical libraries of the world, and Thursday afternoon a symposium on education and training for medical librarianship. Receptions will be held Monday at the British Medical Association House (3:45 p. m.) and at the Royal College of Surgeons of England (8:30 p. m.); Wednesday at the Royal Society of Medicine (6 p. m.); Friday evening at the Royal College of Obstetricians and Gynaecologists, at the Hall of Worshipful Society of Apothecaries, and at Ciba Foundation. A discussion on international cooperation has been scheduled for Saturday morning and visits to the British Museum and to Oxford for Saturday afternoon.

DEATHS IN OTHER COUNTRIES

Dr. Harold Balme died recently after an operation at a hospital near his home in Beckenham, England. As consultant adviser on rehabilitation to the United Nations, the World Health Organization, and the UNICEF, Dr. Balme served as chairman of the UN Technical Working Group on the Rehabilitation of the Handicapped and was instrumental in the establishment and development of the coordinated international rehabilitation program being carried out by the UN and specialized agencies.

CORRECTION

William Beaumont, Pioneer Physiologist.—The paper on this subject by Dr. Frederick Stenn was read before the Midwestern Regional Group of the Medical Library Association instead of the "Medical Section of the American Library Association" as stated in the footnote to this article in THE JOURNAL, July 4, 1953, page 915. The American Library Association does not have a medical section.

EXAMINATIONS AND LICENSURE

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Parts I and II.* All centers where there are five or more candidates. Sept. 8-10 (Part I only). Candidates may file applications at any time, but the National Board must receive them at least six weeks before the date of the examination they wish to take. *Part III.* June 9-26. Examination will be held in each of 31 centers having five or more eligible candidates. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia 4.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various locations, July 16. Final date for filing applications was January 17. Sec., Dr. C. B. Hickcox, 80 Seymour St., Hartford 15.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: All candidates must now pass a written examination. *Written.* Various centers, Sept. 3. *Oral.* Philadelphia, Oct. 16-18. To be eligible, candidate must complete 36 months of training before Oct. 1. Final date for filing applications was May 1. Exec. Sec., Miss Janet Newkirk, 66 East 66th St., New York 21.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* San Francisco, Sept. 30-Oct. 2, Chicago, Nov. 30-Dec. 2. The closing date for acceptance of applications for the San Francisco and Chicago oral examination was April 1. *Written.* October 19. The closing date for acceptance of applications was May 1. Exec. Sec.-Treas., Dr. William A. Werrell, 1 West Main St., Madison 3.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral.* New Haven, October. Final date for filing application is July 1. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, Kingshighway and Euclid Ave., St. Louis.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Written.* Various cities of the United States and Canada, Feb. 5. Application for examination or re-examination, as well as requests for resubmission of case reports, must be made prior to October 1. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: Chicago, Oct. 5-9. *Written.* Various Centers, January 1954. Final date for filing applications is July 1. Sec., Dr. Edwin B. Dunphy, 56 Ivie Road, Cape Cottage, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: Chicago, January 1954. Final date for filing application is August 15. Sec., Dr. Harold A. Sofield, 122 S. Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral.* Chicago, Oct. 5-9. Sec., Dr. Dean M. Lierle, University Hospital, Iowa City.

AMERICAN BOARD OF PATHOLOGY: *Written. Pathologic Anatomy and Clinical Pathology.* Chicago, Oct. 8-10. Sec., Dr. William B. Wartman, 303 E. Chicago Ave., Chicago.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Ann Arbor, June 26-27. Place undecided, Oct. 9-11 (tentative); Indianapolis, November. Exec. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PLASTIC SURGERY: *Entire Examination.* San Diego, Oct. 29-31. Final date for receipt of case reports was June 1. *Entire Examination.* Galveston, April 17-19. Final date for receipt of case reports is Jan. 1. Corres. Sec., Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PROCTOLOGY: *Part II. Oral and Written. Anorectal Surgery and Proctology.* Philadelphia, Sept. 19. Sec., Dr. Louis A. Buie, 102-110 Second Ave. S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: *Oral. Radiology, Roentgenology, Diagnostic Roentgenology and Therapeutic Radiology.* Chicago, Dec. 6-11. Final date for filing application is July 1. Sec., Dr. B. R. Kirklin, 102-110 Second Ave. S.W., Rochester, Minn.

BOARD OF THORACIC SURGERY: *Written.* Various centers throughout the country, September 11. Final date for filing application is July 1. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secretary.

1953 Clinical Session, St. Louis, Dec. 1-4.
1954 Annual Session, San Francisco, June 21-25.
1954 Clinical Session, Miami, Florida, Nov. 30-Dec. 3.
1955 Annual Session, Atlantic City, N. J., June 6-10.
1955 Clinical Session, Boston, Nov. 29-Dec. 2.

AMERICAN CONGRESS OF PHYSICAL MEDICINE, Palmer House, Chicago, Aug. 31-Sept. 4. Dr. Walter J. Zeiter, 30 North Michigan Ave., Chicago 2, Executive Director.

AMERICAN DIETETIC ASSOCIATION, Los Angeles, Aug. 24-28. Miss Ruth M. Yakel, 620 N. Michigan Ave., Chicago 11, Executive Secretary.

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY, Commander and Continental Hotels, Cambridge, Mass., Aug. 17-22. Dr. John A. Abbott, Massachusetts General Hospital, Boston 14, Secretary.

AMERICAN HOSPITAL ASSOCIATION, San Francisco, Aug. 31-Sept. 3. Mr. George Bugbee, 18 East Division St., Chicago 11, Executive Director.

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, Fall Meeting, Yale University, New Haven, Conn., Sept. 7-9. Dr. Carl C. Pfeiffer, 1853 West Polk St., Chicago 12, Secretary.

AMERICAN VETERINARY MEDICAL ASSOCIATION, Royal York Hotel, Toronto, Canada, July 20-23. Dr. J. G. Hardenbergh, 600 South Michigan Blvd., Chicago 5, Executive Secretary.

BIOLOGICAL PHOTOGRAPHIC ASSOCIATION, Hotel Statler, Los Angeles, Aug. 31-Sept. 3. Miss Jane H. Waters, 533 West 57th St., New York 19, Secretary.

GERONTOLOGICAL SOCIETY, Mark Hopkins Hotel, San Francisco, Aug. 25-27. Dr. Nathan W. Shock, Baltimore City Hospitals, Baltimore 24, Secretary.

NATIONAL MEDICAL ASSOCIATION, Nashville, Tenn., Aug. 10-14. Dr. John T. Givens, 1108 Church St., Norfolk 10, Va., Executive Secretary.

POST GRADUATE MEDICAL ASSEMBLY OF SOUTH TEXAS, Shamrock Hotel, Houston, July 20-22. Dr. C. A. Dwyer, 229 Medical Arts Bldg., Houston, Secretary.

REGIONAL MEETINGS, AMERICAN COLLEGE OF PHYSICIANS:
WEST VIRGINIA, White Sulphur Springs, July 24. Dr. Paul H. Revercomb, 1031 Quarrier St., Charleston 1, Governor.

SOCIETY OF AMERICAN BACTERIOLOGISTS, Palace Hotel, San Francisco, Aug. 10-14. Dr. John H. Bailey, Sterling-Winthrop Research Institute, Rensselaer, N. Y., Secretary.

UTAH STATE MEDICAL ASSOCIATION, Salt Lake City, Sept. 10-12. Dr. Homer E. Smith, 42 South Fifth East St., Salt Lake City 2, Secretary.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, The Greenbrier, White Sulphur Springs, July 23-25. Mr. Charles Lively, P. O. Box 1031, Charleston 24, Executive Secretary.

FOREIGN

ASSOCIATION OF SURGEONS OF GREAT BRITAIN AND IRELAND, Leeds, England, May 13-15, 1954. Dr. Henry W. S. Wright, 45 Lincoln's Inn Fields, London W.C.2, England, Honorary Secretary.

CANADIAN MEDICAL ASSOCIATION, Vancouver, B. C., Canada, June 18-22, 1954. Dr. T. C. Routley, 135 St. Clair Ave. W., Toronto 5, Ont., Canada, General Secretary.

CONGRESS OF INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, Chateau Frontenac, Quebec, Canada, October 26-29. Dr. A. William Friend, 515 Nome Ave., Akron 20, Ohio, Chairman, Program Committee.

CONGRESS OF THE INTERNATIONAL ASSOCIATION OF LIMNOLOGY, Cambridge and Windermere, England, Aug. 20-30. For information write: Professor G. C. Hutchinson, Osborn Zoological Laboratory, Yale University, New Haven, Conn., U. S. A.

CONGRESS OF THE INTERNATIONAL LEAGUE AGAINST RHEUMATISM, Geneva, Switzerland and Aix-les-Bains, France, Aug. 23-29. For information write: Dr. W. Tegner, The London Hospital, London E.1, England.

CONGRESS OF THE INTERNATIONAL SOCIETY OF ANGIOLOGY, Lisbon, Portugal, Sept. 18-20. Dr. Henry Haimovici, 105 East 90th St., New York 28, N. Y., U. S. A., Secretary.

CONGRESS OF THE INTERNATIONAL SOCIETY OF SURGERY, Lisbon, Portugal, Sept. 14-20. Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium, General Secretary.

INTERIM MEETING, AERO MEDICAL ASSOCIATION, University of Brussels Medical School, Brussels, Belgium, Sept. 24-27. Dr. Andre Allard, Medical Director of SABENA, 145 Rue Royale, Brussels, Belgium, Secretary.

INTERNATIONAL CONFERENCE ON THROMBOSIS AND EMBOLISM, Basle, Switzerland, July 15-19, 1954. Dr. W. Merz, Chief Medical Officer, Gynecological Clinic, University of Basle, Basle, Switzerland, Hon. Secretary.

INTERNATIONAL CONGRESS OF ACUPUNCTURE, Kolpinghaus, Adolf-Kolping-Strasse 1, Munich, Germany, August 22-25. Dr. G. Bachmann, 29 Lilienstrasse, München 9, Germany, Organizer and Secretary.

INTERNATIONAL CONGRESS OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY, Boston, Mass., U. S. A., Aug. 18-21. Dr. Robert S. Schwab, Massachusetts General Hospital, Boston 14, Mass., U. S. A., Secretary-General.

INTERNATIONAL CONGRESS OF THE EUROPEAN SOCIETY OF HAEMATOLOGY, Amsterdam, Holland, Sept. 8-12. Dr. M. C. Verloop, Maliesingle 15, Utrecht, Holland, Secretary.

INTERNATIONAL CONGRESS ON GENETICS, Bellagio, Italy, August 24-31. Prof. C. Barigozzi, Instituto de Genetica, Universita de Milano, 10 via Celoria, Milan, Italy, Secretary.

INTERNATIONAL CONGRESS OF HIPPOCRATIC MEDICINE, Evian, France, Sept. 3-6. Prof. P. Delore, 13, rue Jarente, Lyon, France, Secretary-General.

INTERNATIONAL CONGRESS FOR HISTORY OF SCIENCE, Jerusalem, Israel, August 3-7. Prof. F. S. Bodenheimer, Hebrew University, Jerusalem, Israel, President.

INTERNATIONAL CONGRESS OF HYDROCLIMATISM AND THALASSOTHERAPY, Dubrovnik, Yugoslavia, May 8-16, 1954. Prof. C. Plavsic, Zeleni Venac 1, Belgrade, Yugoslavia, Secretary General.

INTERNATIONAL CONGRESS OF INTERNATIONAL COLLEGE OF SURGEONS, Sao Paulo, Brazil, April 26-May 2, 1954. Dr. Max Thorek, 1516 Lake Shore Drive, Chicago, Illinois, U.S.A., Secretary-General.

INTERNATIONAL CONGRESS OF LOGOPEDICS AND PHONIATRICS, Zurich, Switzerland, Sept. 1-5. Dr. Deso A. Weiss, 115 East 86th St., New York 28, N. Y., U. S. A., General Secretary.

INTERNATIONAL CONGRESS ON MEDICAL LIBRARIANSHIP, London, England, July 20-25. Mr. W. R. LeFanu, % London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1, England, Chairman.

INTERNATIONAL CONGRESS ON MENTAL HEALTH, University of Toronto, Toronto, Ontario, Canada, Aug. 14-21, 1954. For information write: Executive Officer, International Congress on Mental Health, 111 St. George St., Toronto, Ontario, Canada.

INTERNATIONAL CONGRESS OF MICROBIOLOGY, Rome, Italy, Sept 6-12. For information write: Dr. V. Puntoni, Citta Universitaria, Rome, Italy.

INTERNATIONAL CONGRESS ON OBSTETRICS AND GYNECOLOGY, Geneva, Switzerland, July 26-31, 1954. Dr. H. de Watteville, Maternité Hôpital Cantonal, Geneva, Switzerland, President.

INTERNATIONAL CONGRESS OF PAEDIATRICS, Havana, Cuba, Oct. 12-17. Prof. Felix Hurtado, 5a Avenue 124, Miramar, Havana, Cuba. President.

INTERNATIONAL CONGRESS OF PSYCHOLOGY, Montreal, Canada, June 7-12, 1954. For information write: Prof. H. S. Langfeld, International Union of Scientific Psychology, Eno Hall, Princeton University, Princeton, N. J., U. S. A.

INTERNATIONAL CONGRESS OF RADIOLOGY, Copenhagen, Denmark, July 19-25. Professor Flemming Norgaard, 10 Oster Voldgade, Copenhagen K, Denmark, Secretary General.

INTERNATIONAL CONGRESSES OF TROPICAL MEDICINE AND MALARIA, Istanbul, Turkey, Aug. 28-Sept. 4. Professor Dr. Ihsan Sükrü Aksel, Tunel Meydam, Beyoglu, Istanbul, Turkey, General Secretary.

INTERNATIONAL CONGRESS OF ZOOLOGY, Copenhagen, Denmark, Aug. 5-12. Dr. Anton F. Bruun, The University, Copenhagen, Denmark, Secretary General.

INTERNATIONAL GERONTOLOGICAL CONGRESS, London and Oxford, England, July 12-22, 1954. Prof. R. E. Tunbridge, General Infirmary, Department of Medicine, The University, Leeds, England, President.

INTERNATIONAL LEPROSY CONGRESS, Madrid, Spain, Oct. 3-10. Dr. Felix Contreras, Moreto 15, Madrid, Spain, Secretary.

INTERNATIONAL NEUROLOGICAL CONGRESS, LISBON, Portugal, Sept. 7-12. Prof. Almeida Lima, Avenida do Brazil 53, Lisbon, Portugal, Secretary-General.

INTERNATIONAL OFFICE OF DOCUMENTATION OF MILITARY MEDICINE, Rome, Italy, Oct. 14-18. Colonel Medecin Prof. A. Campana, Office of the Ministero della Difesa-Esercito, Rome, Italy, Secretary.

INTERNATIONAL PHYSIOLOGICAL CONGRESS, Montreal, Canada, Aug. 31-Sept. 4. Dr. A. S. V. Burgen, Dept. of Physiology, McGill University, Montreal, Canada, Secretary.

INTERNATIONAL PSYCHO-ANALYTICAL CONGRESS, Bedford College, Regent's Park, London N.W.1, England, July 26-30. Dr. Ruth S. Eissler, 285 Central Park West, New York 24, N. Y., Hon. Secretary.

INTERNATIONAL SOCIETY FOR THE STUDY OF BIOLOGICAL RHYTHMS, Basle, Switzerland, Sept. 18-19. For information write: Prof. Dr. F. Georgi, Neurologische Universitats-Poliklinik, Socinstrasse 55, Basle, Switzerland.

INTERNATIONAL VETERINARY CONGRESS, Stockholm, Sweden, Aug. 9-15. Prof. Axel Isaksson, Institute of Veterinary Medicine, Stockholm 50, Sweden, Secretary.

JOURNEES MEDICALES, Paris, France, April 21-25, 1954. For information write: Secretariat of the Journees, 12, rue Pierre-Geofroix, Colombes (Seine) France.

LATIN AMERICAN CONGRESS OF OBSTETRICS AND GYNECOLOGY, Buenos Aires, Argentina, Oct. 26-31.

LATIN AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY, Caracas, Venezuela, Feb. 21-25, 1954. Dr. Victorino Marquez Reveron, Centro Medico, Caracas, Venezuela, Secretary-General.

PACIFIC SCIENCE CONGRESS, Quezon City and Manila, Philippines, Nov. 16-28. Dr. Patrocinio Valenzuela, College of Pharmacy, University of the Philippines, Quezon City, Philippines, Secretary-General.

PAN AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY, Mexico, D.F., Mexico, Feb. 28-March 4, 1954.

PAN AMERICAN MEDICAL WOMEN'S ALLIANCE, Beekman Towers Hotel, New York, N. Y., Sept. 24-Oct. 1. Dr. Ina Marsh, 140 Linwood Ave., Buffalo, N. Y., U. S. A., Registration Chairman.

PERSIAN GULF MEDICAL SOCIETY, Dhahran, Saudi Arabia, Dec. 7-8. Dr. N. J. Conan Jr., Department of Internal Medicine, Arabian American Oil Company, Dhahran, Saudi Arabia, Secretary.

SECTIONAL MEETING, AMERICAN COLLEGE OF SURGEONS, London, England, May 17-19, 1954. Dr. Michael L. Mason, 40 East Erie St., Chicago 11, Ill., U. S. A., Secretary.

WORLD CONFERENCE ON MEDICAL EDUCATION, British Medical Association House, Tavistock Square, W.C.1, London, England, Aug. 22-29. Secretariat: World Medical Association, 2 East 103d St., New York 29, N. Y., U. S. A.

WORLD CONGRESS OF THE WORLD CONFEDERATION FOR PHYSICAL THERAPY, London, England, Sept. 7-12. Miss M. J. Neilson, Chartered Society of Physiotherapy, Tavistock House, South, Tavistock Square, London, W.C.1, England, Secretary.

WORLD MEDICAL ASSOCIATION, The Hague, Netherlands, Aug. 31-Sept. 7. Dr. Louis H. Bauer, 345 East 46th St., New York 17, N. Y., Secretary-General.

DEATHS

Eckert, George Arthur ⊕ Captain, U. S. Navy, retired, Newport, R. I.; born in Newport, R. I., Aug. 10, 1889; University of Vermont College of Medicine, Burlington, 1914; entered active service in the medical corps of the U. S. Navy on Aug. 1, 1917; during World War I served at the Naval Hospital in Queenstown, Ireland; chief of surgical service at many naval hospitals and aboard hospital ships, including the U. S. S. Solace at Pearl Harbor; during World War II served in the Pacific area aboard the Solace, at naval hospitals in the United States, and at various commissioning units of Navy mobile hospitals; in 1943 served as the senior medical officer of the Hospital Section of Cub no. 8; placed on retired list of the Navy on Jan. 1, 1945; retained on active duty until Jan. 1, 1946, when he was released to inactive duty; member of the founders group of the American Board of Surgery; fellow of the American College of Surgeons; affiliated with the Newport Hospital and the U. S. Naval Hospital, where he died June 5, aged 63, of infarction of the myocardium.

McCord, Clinton Preston ⊕ Albany, N. Y.; born in Elverson, Pa., April 20, 1881; University of Pennsylvania School of Medicine, Philadelphia, 1912; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychoanalytic Association, American Psychosomatic Society, American Psychiatric Association, and the American Orthopsychiatric Association; for many years director of health education in the public schools; formerly on the faculty of Albany Medical College; for several years consultant in psychiatry to the state health department; served as consulting psychiatrist at the Berkshire Industrial Farm at Canaan; author of numerous monographs on behavior delinquency and war neuroses; died May 10, aged 72.

Barlow, Brian Ethelbert ⊕ Dermott, Ark.; born in Dermott, Oct. 29, 1909; University of Arkansas School of Medicine, Little Rock, 1937; fellow of the American College of Chest Physicians, American Trudeau Society, Southwest Surgical Congress, and the American Academy of General Practice; past president of the Arkansas Tuberculosis Association and the Chicot County Medical Society; associate, International College of Surgeons; member of the New Orleans Postgraduate Medical Assembly; member of the school board, chamber of commerce, and the city parks and recreation commission; director of the Dermott State Bank; past president of the Rotary Club; on the staff of St. Mary's Hospital; died May 21, aged 43, of coronary thrombosis.

Slemons, Clyde Calderwood ⊕ Grand Rapids, Mich.; born in Cedar Springs, Mich., Dec. 31, 1874; Detroit College of Medicine, 1905; for many years health officer of Grand Rapids, state health commissioner, and member of the state council of health; first school physician; past president of the Michigan Public Health Association; member of the American Public Health Association; assistant professor of preventive medicine and public health at Wayne University College of Medicine in Detroit from 1936 to 1938; in 1931 received the degree of doctor of public health from his alma mater; on the courtesy staff of the Butterworth Hospital; died May 7, aged 78, of arteriosclerotic myocardial degeneration with congestive failure.

Moore, Roy Seeley, Syracuse, N. Y.; Syracuse University College of Medicine, 1912; clinical professor emeritus of otolaryngology at his alma mater; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology and the American Laryngological, Rhinological and Otological Society; fellow of the American College of Surgeons; affiliated with General Hospital and the Hospital of the Good Shepherd; died in Fort Lauderdale, Fla., May 26, aged 68, of coronary occlusion and arteriosclerotic heart disease.

⊕ Indicates Member of the American Medical Association.

Albert, Simon, Providence, R. I.; Harvard Medical School, Boston, 1922; specialist certified by the American Board of Radiology; member of the New England Roentgen Ray Society; served during World Wars I and II; affiliated with the Memorial Hospital in Pawtucket, Miriam Hospital and past president of its staff, and the Rhode Island Hospital, where he died May 3, aged 56, of coronary heart disease and hemorrhage from a duodenal ulcer.

Barndollar, William Piper ⊕ Pittsburgh; University of Pennsylvania Department of Medicine, Philadelphia, 1902; member of the American Laryngological, Rhinological and Otological Society; affiliated with Allegheny General Hospital, where he died May 11, aged 73, of general arteriosclerosis.

Bauder, George Washington ⊕ Harrisburg, Pa.; Rush Medical College, Chicago, 1903; affiliated with Harrisburg Hospital; died in Harrisburg Polyclinic Hospital April 21, aged 74, of cancer.

Bausman, Albert J. ⊕ Piqua, Ohio; Medical College of Ohio, Cincinnati, 1895; on the staff of the Piqua Memorial Hospital; died May 27, aged 87, of acute coronary occlusion.

Beasley, Charles Wesley ⊕ Lyndon, Kan.; Missouri Medical College, St. Louis, 1894; for many years county health officer; died April 7, aged 82.

Bennett, Andrew William ⊕ Iowa City; State University of Iowa College of Medicine, Iowa City, 1918; past president of the Johnson County Medical Society; served during World War I; affiliated with Mercy Hospital; died April 11, aged 62, of coronary thrombosis.

Birch, Charles E., White Plains, N. Y.; New York Homeopathic Medical College and Hospital, New York, 1891; served as village health officer and as county coroner; formerly on the staff of the White Plains Hospital; died in Katonah May 11, aged 90, of coronary artery occlusion.

Brown, Arthur Aloysius ⊕ Millbury, Mass.; Jefferson Medical College of Philadelphia, 1906; an Associate Fellow of the American Medical Association; chairman of the local board of health and school physician; resigned in 1950 as trustee of the Millbury Savings Bank; died in St. Vincent Hospital, Worcester, April 7, aged 71, of coronary thrombosis and pulmonary fibrosis.

Bull, Charles Henry, Newport Beach, Calif.; Victoria University Medical Department, Coburg, Ontario, Canada, 1892; died April 19, aged 86.

Carberry, Blaine Edward ⊕ Ford City, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1932; served during World War II; on the staff of the Armstrong County Memorial Hospital in Kittanning; died March 30, aged 47, of coronary occlusion.

Carson, Rollett Andrew ⊕ Cleveland; University of Toronto Faculty of Medicine, Toronto, Canada, 1922; affiliated with St. Luke's Hospital; died May 23, aged 56, of coronary thrombosis.

Chandler, Melvin Elwell ⊕ Flint, Mich.; University of Michigan Homeopathic Medical School, Ann Arbor, 1906; died in St. Joseph's Hospital April 25, aged 81, of bronchopneumonia and arteriosclerosis.

Chang, Wah Kai ⊕ Honolulu, Hawaii; Rush Medical College, Chicago, 1921; fellow of the American College of Surgeons; served as vice-president of the Hawaii Territorial Medical Association; past president of the Honolulu County Medical Society; on the staff of St. Francis Hospital, Kapiolani Maternity and Gynecological Hospital, and Queen's Hospital, where he died March 22, aged 59, of coronary thrombosis.

Clecak, Nicholas Jeffries ⊕ Oakland, Calif.; Rush Medical College, Chicago, 1918; died May 19, aged 60, of bronchogenic carcinoma.

Cochran, John Howard ✦ Cape Girardeau, Mo.; Barnes Medical College, St. Louis, 1911; formerly member of the board of health of Cape Girardeau; past president of the Cape Girardeau County Medical Society; decorated with the British Military Cross for service in the British Division during World War I; died May 4, aged 63, of subarachnoid hemorrhage.

Cockrell, Eugene Peyton ✦ Kalispell, Mont.; Washington University School of Medicine, St. Louis, 1906; for many years city health officer; veteran of the Spanish-American War; died April 17, aged 73, of cancer.

Cowan, Arthur ✦ Chenango Bridge, N. Y.; Julius Maximilians-Universität Medizinische Fakultät, Wurzburg, Bavaria, Germany, 1906; died in the Broome County Tuberculosis Hospital March 10, aged 63, of cerebral vascular accident.

Crandall, Henry Noble, Conneaut, Ohio; George Washington University School of Medicine, Washington, D. C., 1904; served during World War I; on the staff of the Conneaut Hospital, where he died April 13, aged 75, of congestive heart failure.

Cruickshank-Bailey, Jean ✦ Greensburg, Pa.; University of Toronto Faculty of Medicine, Toronto, Canada, 1898; Trinity Medical College, Toronto, 1900; died April 20, aged 85, of arteriosclerotic heart disease.

Cummins, William Taylor, San Francisco; University of Pennsylvania Department of Medicine, Philadelphia, 1902; specialist certified by the American Board of Pathology; member of the American Society of Clinical Pathologists, of which he was vice-president; for many years secretary of the Pacific Association of Railway Surgeons; served as assistant demonstrator of pathology at his alma mater; on the staff of the Southern Pacific Hospital, where he died May 5, aged 73, of tumor of the brain.

Davidson, Joseph Samuel ✦ Forrest City, Ark; Vanderbilt University School of Medicine, Nashville, Tenn., 1910; served during World War I; died April 15, aged 65, of heart disease.

Davies, George William ✦ Verona, N. J.; Baltimore Medical College, 1905; school physician for Verona and Cedar Grove; served during World War I; psychiatrist for the Verona Selective Service Board during World War II; affiliated with Essex County Overbrook Hospital in Cedar Grove and the Mountainside Hospital in Montclair, where he died May 24, aged 74, of carcinoma of the esophagus and cardiac decompensation.

Dowlen, Willard Madell, Nashville, Tenn.; University of Nashville Medical Department, 1898; died March 21, aged 82, of chronic myocarditis.

Du Bois, William John ✦ Kaleva, Mich.; University of Georgia School of Medicine, Augusta, 1899; for many years surgeon for the Kent County Welfare Board; formerly practiced in Grand Rapids, where he was on the staff of the Butterworth Hospital; died May 9, aged 80, of cerebral hemorrhage.

Eber, Albert H. ✦ Lieut. Col., U. S. Army, retired, Detroit, Mich.; Detroit College of Medicine, 1897; entered the medical corps of the U. S. Army as a major on July 1, 1920, and retired Dec. 30, 1927, for disability in line of duty; promoted to lieutenant colonel on June 21, 1930, under the Act of June 21, 1930; veteran of the Spanish-American War and World War I; for many years medical superintendent of the Leland Sanatorium in Ypsilanti, Mich.; died in the Receiving Hospital May 17, aged 77.

Ellet, William Clinton, Benton Harbor, Mich.; University of Michigan Medical School, Ann Arbor, 1921; at one time mayor; served during World War II; member of the state board of registration in medicine; formerly city health officer; affiliated with Mercy Hospital, where he died April 4, aged 56, of carcinoma of the larynx.

Farnum, Earl P. ✦ Sibley, Iowa; State University of Iowa College of Homeopathic Medicine, Iowa City, 1898; died May 16, aged 75, of cerebral hemorrhage.

Ferguson, Ward Smith ✦ Grand Rapids, Mich.; Chicago College of Medicine and Surgery, 1910; on the staffs of the Blodgett Memorial Hospital and St. Mary's Hospital; cofounder of the Ferguson-Droste-Ferguson Rectal Clinic and Hospital, where he died April 16, aged 66.

Fuerste, Frederick ✦ Dubuque, Iowa; State University of Iowa College of Medicine, Iowa City, 1920; died May 12, aged 58, of carcinoma of the lung.

George, Raymond Horace ✦ Cincinnati; Loyola University School of Medicine, Chicago, 1916; awarded British Military Cross for bravery during World War I; physician for the Cincinnati regional office of the Veterans Administration; died in the Good Samaritan Hospital April 19, aged 66.

Glaze, Kenneth Franklin ✦ Temple, Texas; St. Louis University School of Medicine, 1923; fellow of the American College of Physicians; affiliated with VA Center; died April 6, aged 54, of fatty liver.

Griffin, Alonzo P. Tracy, Calif.; University of Tennessee College of Medicine, Memphis, 1891; died in Saratoga March 27, aged 87.

Mercer, Mifflin W. ✦ Downington, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1910; for many years secretary of the board of health of Downington and physician for the Pennsylvania Railroad; served on the staffs of the Chester County Hospital and Memorial Hospital of Chester County in West Chester; died April 17, aged 75, of uremia.

Miller, Arthur, L., Gilliam, Mo.; Missouri Medical College, St. Louis, 1896; died April 9, aged 87.

Miller, Elwood, Springfield, Ohio; Medical College of Ohio, Cincinnati, 1887; served during World War I; died April 13, aged 88, of bilateral lobar pneumonia and generalized arteriosclerosis.

Morrison, Charles Carr Jr. ✦ Bar Harbor, Maine; Harvard Medical School, Boston, 1918; fellow of the American College of Surgeons; served as police surgeon in Palm Beach, Fla.; honorary officer of the Bar Harbor police and fire departments; affiliated with St. Joseph Hospital in Bangor and Eastern Memorial Hospital in Ellsworth; died April 13, aged 59.

Morton, Charles Rufus, Madisonville, Ky.; Hospital College of Medicine, Louisville, 1906; for many years health officer; died March 22, aged 75.

Motley, Jewett Palmar ✦ Birmingham, Ala.; Rush Medical College, Chicago, 1937; served during World War II; affiliated with South Highlands Infirmary, Jefferson-Hillman Hospital, East End Memorial Hospital, Highland Avenue Baptist Hospital, and the West End Baptist Hospital, where he died April 22, aged 46, of carcinoma of the small intestine.

Mozingo, Arvine Earl ✦ Indianapolis; Indiana University School of Medicine, Indianapolis, 1913; served during World War I; died in the Robert W. Long Hospital April 24, aged 72, of retroperitoneal hematoma and anuria due to general arteriosclerosis.

Mullarky, Hugh, Long Beach, Calif.; State University of Iowa College of Medicine, Iowa City, 1889; served during World War I; formerly associated with the Indian Service; died April 13, aged 88.

Newman, Abraham Jacob ✦ Jersey City, N. J.; Cornell University Medical College, New York, 1910; died April 19, aged 66.

Newman, Lester ✦ San Francisco; Medical Department of the University of California, San Francisco, 1908; member of the Industrial Medical Association; died April 25, aged 70, of hypertensive and arteriosclerotic heart disease.

Northridge, William Albert, San Diego, Calif.; Long Island College Hospital, Brooklyn, 1882; fellow of the American College of Physicians; formerly on the faculty of his alma mater; died April 23, aged 92, of congestive heart failure and arteriosclerosis.

Orton, Zenas Van Duzen, Salem, N. Y.; Albany (N. Y.) Medical College, 1907; for many years health officer; died in New York City in March, aged 70.

Parks, William H. ✦ Petoskey, Mich.; Detroit College of Medicine, 1912; on the staff of the Lockwood General Hospital; died April 14, aged 65, of coronary occlusion.

Parsegan, Jacob Hohaness, San Leandro, Calif.; College of Physicians and Surgeons, Medical Department of Columbia College, New York, 1895; died March 17, aged 81, of cerebral thrombosis and arteriosclerosis.

Perrin, Deckard Leroy ✦ Seymour, Ind.; Hospital College of Medicine, Louisville, Ky., 1898; affiliated with Schneck Memorial Hospital; died in Madison April 6, aged 83, of cerebral arteriosclerosis.

Prestridge, Barney Bertrand ✦ Donna, Texas; University of Texas School of Medicine, Galveston, 1944; served during World War II; died April 7, aged 31.

Rosenberg, Nicholas L. ✦ Pittsburgh; University of Louisville (Ky.) Medical Department, 1910; died in the Western Pennsylvania Hospital May 7, aged 66, of myocardial infarction.

Rosenfeld, Ernst ✦ Penn Yan, N. Y.; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1913; on the staff of the Soldiers and Sailors Memorial Hospital, where he died April 6, aged 67, of acute urinary suppression.

Rude, Emerson Waterbury ✦ Utica, N. Y.; New York Homeopathic Medical College and Hospital, New York, 1902; past president of the Herkimer County Medical Society; formerly practiced in Ilion, where he was affiliated with Ilion Hospital; served on the staffs of the Herkimer (N. Y.) Memorial Hospital and the Utica (N. Y.) Memorial Hospital; died April 25, aged 76, of heart disease and cancer.

Sandperl, Harry ✦ St. Louis; Washington University School of Medicine, St. Louis, 1908; fellow of the American College of Surgeons; senior instructor in surgery at St. Louis University School of Medicine; affiliated with St. Mary's Group of Hospitals, St. Louis City Hospital, and Jewish Hospital, where he died May 10, aged 68, of carcinoma.

Schlein, Julius, Tampa, Fla.; Long Island College Hospital, Brooklyn, 1906; formerly a pharmacist; on the staff of the Unity Hospital; died May 7, aged 84, of uremia, arteriosclerotic nephritis, myocarditis, and coronary sclerosis.

Schneck, Sereno Watson ✦ Mount Carmel, Ill.; Northwestern University Medical School, Chicago, 1898; died April 21, aged 78.

Schnitzer, Johann Otto, Wichita, Kan.; University of Kansas School of Medicine, Kansas City, 1951; died April 12, aged 32.

Scott, Zachariah James, Brownsville, Tenn.; Kentucky School of Medicine, Louisville, 1891; served during World War I; on the staff of the Haywood County Memorial Hospital, where he died April 4, aged 89, of carcinoma of the lungs.

Seaman, Benjamin Franklin, Altamonte Springs, Fla.; Albany (N. Y.) Medical College, 1905; formerly on the staff of the Metropolitan Life Insurance Company Sanatorium in Mount McGregor; died April 6, aged 69, of acute coronary occlusion and arteriosclerotic heart disease.

Sibila, Alvin Oscar ✦ Cleveland; Western Reserve University School of Medicine, Cleveland, 1917; served during World War I; member of the Academy of Medicine of Cleveland and the Cleveland Health Museum; for many years member of the city board of health; affiliated with St. John's Hospital and the Fairview Park Hospital, where he died May 12, aged 60, of cerebral thrombosis.

Siegel, Charles Milton ✦ Cincinnati; Marquette University School of Medicine, Milwaukee, 1926; member of the American College of Chest Physicians and the American Trudeau Society; instructor in medicine at the University of Cincinnati College of Medicine; on the staff of the Jewish Hospital; died May 11, aged 52, of rheumatic heart disease.

Sleeper, Frank Warren ✦ Franklin, N. H.; Harvard Medical School, Boston, 1901; member of the Massachusetts Medical Society; died April 3, aged 81, of coronary thrombosis.

Sleet, Joseph Allen, Tucson, Ariz.; Kentucky School of Medicine, Louisville, 1903; died in the VA Hospital May 2, aged 72, of pulmonary emphysema.

Smith, A. Macrae Jr. ✦ Bellingham, Wash.; McGill University Faculty of Medicine, Montreal, Canada, 1938; served during World War II; died May 3, aged 43, of injuries received in an automobile accident.

Switzer, David M. ✦ Little Rock, Ark.; University of Arkansas School of Medicine, Little Rock, 1908; served on the staff of the Baptist Hospital; died April 24, aged 86, of pneumonia.

Tarpinian, Haroutune Asadour ✦ Fresno, Calif.; American University of Beirut School of Medicine, Syria, 1914; on the staff of the Community Hospital, where he died April 30, aged 62, of cerebral hemorrhage.

Toole, John Edward, Branford, Conn.; Yale University School of Medicine, New Haven, 1920; member of the American Urological Association; fellow of the American College of Surgeons; at one time in charge of medical supplies for American Relief Administration in Russia; served during World War II; died April 19, aged 57, of coronary thrombosis.

Turney, Lester Ferris, Windsor, Conn.; Yale University School of Medicine, New Haven, 1902; town health officer; died in Hartford Hospital April 14, aged 75, of anterior myocardial infarction.

Wagoner, Robert Henry ✦ Colburn, Ind.; Medical College of Indiana, Indianapolis, 1903; past president of the Tippecanoe County Medical Society; served during World War I; affiliated with St. Elizabeth Hospital and LaFayette Home Hospital in LaFayette; died April 29, aged 79, of coronary occlusion.

Wahlen, John Albert ✦ Montebello, Calif.; College of Medical Evangelists, Loma Linda and Los Angeles, 1924; member of the American Academy of General Practice; affiliated with White Memorial Hospital in Los Angeles, Garfield Hospital, Monterey Park, and the Beverly Community Hospital; died in the California Hospital in Los Angeles, March 27, aged 60, of bronchogenic carcinoma.

Walker, Robert Irving, New Bedford, Mass.; Boston University School of Medicine, 1914; served overseas during World War I; died in Truesdale Hospital, Fall River, March 12, aged 83.

Walker, Theodore Lee, St. Louis; University of West Tennessee College of Medicine and Surgery, Memphis, 1914; served on the staffs of the Peoples Hospital, St. Mary's Infirmary, and Homer G. Phillips Hospital; died April 30, aged 68, of myocardial infarction.

Waterman, Isaiah John, Los Angeles; State University of Iowa College of Medicine, Iowa City, 1909; died March 31, aged 68, of atelectasis.

Watkins, Otis Lee, Rustburg, Va.; University College of Medicine, Richmond, 1907; for many years county coroner; served during World War I; medical examiner for the draft board during World War II; affiliated with Lynchburg General Hospital and Virginia Baptist Hospital; died in the Memorial Hospital April 28, aged 68, of cerebral hemorrhage.

Werner, Robert Frederic, Downey, Calif.; University of Minnesota Medical School, Minneapolis, 1927; died April 29, aged 52.

Willis, Palestine T., Beaver Dam, Ky.; Louisville (Ky.) Medical College, 1904; died April 9, aged 79, of coronary thrombosis.

Wilson, Harry Edmond ✦ Port Orchard, Wash.; College of Physicians and Surgeons, Baltimore, 1905; served on the staffs of the Harrison Memorial and Puget Sound hospitals in Bremerton; died April 4, aged 74, of coronary thrombosis.

Young, Jack Rufus, Florala, Ala.; Tulane University of Louisiana School of Medicine, New Orleans, 1946; served during World War II; died April 23, aged 31, of leukemia.

GOVERNMENT SERVICES

ARMY

Dr. Smadel Honored.—The University of Chicago recently presented the Howard Ricketts Medal to Dr. Joseph E. Smadel, scientific director of the Army Medical Service Graduate School, Washington, D. C., for his work with antibiotics in the treatment of typhus. Dr. Smadel has been chief of the department of virus and rickettsial diseases since 1946 and technical director of research (communicable and parasitic diseases) since 1950. He is also visiting lecturer in virology at the University of Maryland School of Medicine, Baltimore. He has been director of the commission on immunization, Armed Forces Epidemiological Board, and a member of the virus and rickettsial study section, United States Public Health Service, since 1946 and a member of the committee on virus research and epidemiology and research fellowship in virology, National Foundation for Infantile Paralysis, since 1948. Dr. Smadel holds the U. S. Army Typhus Commission Medal, the Gordon Wilson Medal, and the Exceptional Civilian Service Award.

Personal.—Major Gen. William E. Shambora, Chief Surgeon, U. S. Army, Far East, was honored April 9 as one of the eight alumni chosen by Georgetown University Alumni Association for the 1953 John Carrol Distinguished Service award. In the absence of General Shambora, the Surgeon General designated Col. Floyd L. Wergeland to receive the award for the general.

NAVY

Course for Reserve Officers in Field Medicine.—A two week course in field medicine for inactive reserve medical department officers of the 11th, 12th, and 13th Naval Districts will convene at the marine barracks, Camp Joseph H. Pendleton, Oceanside, Calif., Aug. 17, 1953. Practical instruction in medical matériel logistics, preventive medicine in the field, professional treatment in emergencies, and medical organization with fleet marine units are included. In addition, the trainee will receive practical instruction of a military nature, including the maintenance and use of small arms, items of individual field equipment, and practical march and bivouac routines. Inactive naval reserve medical corps, medical service corps, and hospital corps officers residing in the 11th, 12th, and 13th Naval Districts who desire to attend this course should submit requests to the commandant of the home Naval District at the earliest possible date. Bachelor quarters will be available, and working uniform is required. Attendance will not, in any way, increase the possibility of involuntary recall to active duty. Eligible officers may attend this course on active duty with training orders in a pay status.

PUBLIC HEALTH SERVICE

New International Vaccination Certificates.—The new International Certificates of Vaccination form, which will enable international travelers to complete immunization requirements more expeditiously, will be ready for use about July 1, 1953. This form supersedes the present International Certificate of Inoculation and Vaccination, PHS-731 (FQ), and provides an official record of compliance with vaccination requirements, acceptable to all nations governed by the International Sanitary Regulations, which went into effect last October. It contains vaccination certificates for smallpox, yellow fever, and cholera, and space to record other immunizations. At present vaccination against typhus and plague is not required.

With the new form, a recording of the results of the smallpox vaccination is no longer necessary, except in cases of primary vaccination. In cases of revaccination the smallpox certificate becomes valid immediately, whereas previously a 14 day wait was required. The cholera certificate in the new form becomes valid six days after the first injection. The old form required that the series be completed. The type of vaccine being used in this country provides maximum protection only after the second injection, and the attention of international travelers will be called to the advisability of taking this second shot. The yellow fever vaccination certificate in the new form is valid for six years.

Smallpox and cholera certificates will be certified by local health officers as in the past; however, health officers must use their official stamps; if they do not have one, they should prepare a special stamp for the purpose of certifying these documents. On the new form the signature of the health officer is not necessary, and signature alone is not valid. Yellow fever vaccination certificates issued in the United States are valid in international travel only when the inoculation is obtained from a yellow fever vaccination center designated by the U. S. Public Health Service.

The Public Health Service plans to distribute the International Certificates of Vaccination with passport application forms through clerks of the court and from passport agencies located in Boston, New York City, San Francisco, New Orleans, Chicago, and Washington, D. C., beginning about July 1. Thus, prospective travelers will have more time for immunizations than under the present system, which provides the form upon issuance of a passport. Persons going into countries that do not require a passport may obtain the form from local or state health departments or from facilities of the Public Health Service. The certificate may be obtained also from the Superintendent of Documents, Government Printing Office, Washington 25, D. C., at a cost of $.05, or $1.50 for 100 copies delivered to the same address. Organizations wishing to print their own certificates must obtain the written permission of the Division of Foreign Quarantine, Epidemiology and Immunization Branch, Public Health, Washing 25, D. C.

The old form will be accepted in international travel until the expiration date of the recorded vaccinations. Agencies having a supply of this form may continue to distribute them until their stock is exhausted. When the old form is used its specifications with regard to smallpox vaccination must be complied with, but the new regulations with regard to yellow fever and cholera certification may be applied. Under the new regulations, the Department of Defense will issue its own certificate to military personnel on active duty; however, military dependents must continue to use the new International Certificates of Vaccination.

Superior Service Award.—Dr. Henry M. Freidman of the Public Health Service has just received the Superior Service Award of the Department of Health, Education, and Welfare. The award, the highest given by the department, was presented by Secretary Oveta Culp Hobby. Dr. Freidman, who is retiring after more than 45 years of service, is a medical supervisor on the staff of the U. S. Foreign Quarantine Service, Port of New York. Secretary Hobby said, "He has amply earned the gratitude and esteem of his countrymen. As a Foreign Quarantine Officer, he has worked with his fellow officers in the vital job of guarding our shores against disease and pestilence. It is no exaggeration to say that our country is safer and healthier because of the skill and devotion of such men." Dr. Freidman practiced medicine near his home on the Lower East Side of New York until 1907, when he received an appointment with the U. S. Public Health Service. For many years, he has been a leader in developing programs for the care of dependent children and is, at present, director of medical care for the Jewish Child Care Association of New York.

Laboratory Courses.—Schedules of laboratory refresher training courses to be given at the Venereal Disease Research Laboratory, Chamblee, Ga., during the fiscal year, July 1, 1953, to June 30, 1954, have been announced as follows:

Dates	Courses	Duration, Weeks
Aug. 17-18, 1953	Serology of syphilis	2
Sept. 17-28, 1953	Serology of syphilis	2
Oct. 5-16, 1953	* Management and control of syphilis serology by the regional laboratory	2
Oct. 19-23, 1953	† Laboratory diagnosis of venereal disease	1
Oct. 26 to Nov. 6, 1953	Serology of syphilis	2
Nov. 9-20, 1953	Preparation and standardization of cardiolipin antigens used in serologic tests for syphilis	2
Dec. 7-18, 1953	Serology of syphilis	2
Jan. 11-22, 1954	Serology of syphilis	2
Feb. 8-19, 1954	Serology of syphilis	2
March 8-19, 1954	Serology of syphilis	2
April 5-16, 1954	Serology of syphilis	2
May 3-14, 1954	Serology of syphilis	2
May 17-28, 1954	Preparation and standardization of cardiolipin antigens used in serologic tests for syphilis	2

* This course, designed for assistant laboratory directors and senior laboratory staff members, includes review of interlaboratory training programs, regional laboratory evaluation studies, laboratory inspection procedures, demonstration of antigen check testing, and control serum preparation.

† This course is designed for P. H. S. physicians, laboratory directors, and assistant laboratory directors.

Correspondence should be sent to: Director, Venereal Disease Research Laboratory, P. O. Box 185, Chamblee, Ga.

Dr. Wilder Retires.—Dr. Russell Wilder, director of the National Institute of Arthritis and Metabolic Diseases at Bethesda, Md., brought to a close a 45 year career when he retired, for reasons of health, on July 1. An internationally known nutritionist and authority on diabetes, Dr. Wilder became the first director of the National Institute of Arthritis and Metabolic Diseases shortly after its creation in 1950. He directed an intensive research program against arthritis, rheumatism, and metabolic diseases that included laboratory research at Bethesda, administration of grants in support of research and training in nonfederal institutions, and preparation for clinical investigations in the new clinical center of the National Institutes of Health that just admitted its first patients.

Before serving with the arthritis institute, Dr. Wilder was with the Mayo Foundation and Clinic, Rochester, Minn., from 1919 to 1950. In 1940, he was chairman of the committee on medicine of the National Research Council in which he organized the food and nutrition board. Later he served as chief of the civilian food requirements branch, War Food Administration. He was a special consultant to the research facilities planning committee of the National Institutes of Health in 1950. For 20 years he was a member of the American Medical Association's Council on Foods and will be remembered for his part in bringing about the general acceptance and use of enriched white flour and bread. During World War I he served in the Army as a medical officer. Dr. and Mrs. Wilder will return to their home in Rochester.

Gordon to Head National Leprosarium.—Dr. Eddie M. Gordon has been appointed Medical Officer in Charge of the U. S. P. H. S. Hospital (National Leprosarium), Carville, La. Dr. Gordon succeeds Dr. Frederick A. Johansen, who retired June 1 after 29 years of service at Carville. Dr. Gordon comes to Carville from Chicago, where he has been in charge of the local U. S. P. H. S. Hospital. The retiring medical officer, Dr. Johansen, participated actively in the evolution of the modern sulfone therapy and later guided the installation and organization of the hospital's community activities and rehabilitation services. He is widely recognized as an authority on leprosy.

Personal.—Dr. Myron D. Miller has been appointed medical officer in charge of the U. S. Public Health Service Hospital, Seattle, effective Aug. 1, succeeding Dr. William W. Nesbitt, who died suddenly on May 7.——Dr. David J. Zaugg has been appointed medical officer in charge of the U. S. Public Health Service Hospital, Chicago, effective July 1, succeeding Dr. Eddie M. Gordon, recently assigned to head the U. S. Public Health Service Hospital (National Leprosarium) at Carville, La.

VETERANS ADMINISTRATION

Vacancies for Occupational Therapists.—The Veterans Administration has many vacancies for occupational therapists and physical therapists at VA centers and hospitals throughout the United States. These vacancies are at grade GS-5, with the salary of $3,410 to $4,160 per annum, and grade GS-7, with the salary of $4,205 to $4,955 per annum. Persons thus employed enjoy excellent employment conditions and also have an essential part in aiding their government. Further information may be obtained from Mr. Jerome J. Deutsch or Mr. Walter J. Shanley by calling Main 5-7400, extension 369 or 371, Brooklyn 1, or from the Executive Secretary, Committee of Expert Examiners, Veterans Administration, Washington 25, D. C.

Personal.—Dr. Alexander W. Kruger of Washington, D. C., has been appointed manager of the Veterans Administration Hospital at Manchester, N. H., succeeding Dr. Bernard L. Allen. Dr. Allen has been transferred to the new VA Hospital at West Haven, Conn. Dr. Kruger was born in Russia but was educated in the United States. He practiced medicine in New York City nine years (1925-1934), and from 1948 through 1951 was general medical superintendent, Department of Hospitals, City of New York. He served as a lieutenant commander in the Navy Medical Corps from June, 1944, to November, 1945.——The Veterans Administration announces the appointment of Dr. Stewart T. Ginsberg of Marion, Ind., as manager of the new 956 bed neuropsychiatric hospital nearing completion at Pittsburgh and of Dr. Louis M. Hohman of Indianapolis as manager of the 200 bed general medical and surgical hospital at Clarksburg, W. Va.

MISCELLANEOUS

Atoll Research Program.—The Coral Atoll Research Program sponsored by the National Academy of Sciences-National Research Council, with financial assistance from the Office of Naval Research, is being continued with the despatch from Honolulu of three scientists to Ifaluk Atoll in the Western Carolinas; in September, four more men will go to Ifaluk. The field work, which will be concluded in November, will parallel the pattern of ecologic investigations that have been made at the atolls of Arno in the Marshalls, Onotoa in the Gilberts, and Raroia in the Tuamotus as part of a five year program of basic research. Results will be correlated with other atoll research. This program is also associated with an atoll project of the six government South Pacific Commission concerned with problems affecting the economy of atoll peoples in Pacific areas administered by Australia, France, New Zealand, Netherlands, United Kingdom, and the United States. Ifaluk is a small atoll about 400 miles south of Guam, with a land area of one-half a square mile, and with 250 inhabitants that have had little contact with other islands. In 1948, E. G. Burrows and M. E. Spiro spent several months there under a Pacific Science Board project supported by the Office of Naval Research as part of a Coordinated Investigation of Micronesian Anthropology. Dr. Burrows, who is professor of anthropology at the University of Connecticut, will return to Ifaluk as the leader of this summer's team.

Foreign Scientific Visitors.—The National Academy of Sciences-National Research Council, Office of International Relations, is receiving an increased amount of information on the travel plans of foreign scientists and engineers who plan to visit the United States, and it has arranged a list of these visitors, together with their itinerary, in order that any group or society desiring to contact them for the purpose of arranging lecture engagements or to visit their institutions may do so. Further information may be obtained by writing to the above office at 2101 Constitution Ave., Washington 25, D. C.

FOREIGN LETTERS

DENMARK

Cytological Tests for Lung Cancer.—At the Thoracic Surgery Department of the Copenhagen City Hospital of Øresund, directed by Dr. Tage Kjaer, much work has been done recently in diagnosis of lung cancer by the microscopic examination of presumptive tumor cells found in the bronchi and sputum. Valuable pioneer work has been done in this field by Dr. H. H. Wandall, whose study, published in 1944, showed that tumor cells could be found in 84% of patients suffering from primary bronchogenic cancer. Commenting on this study in *Nordisk medicin* for May 8, 1953, Dr. J. Iversen emphasizes the importance of Wandall's investigations because they included a large number of patients who were not suffering from malignant disease of the lungs and, therefore, who served as controls. Dr. Iversen's study from the above-mentioned Thoracic Surgery Department concerned 124 cases of primary bronchogenic cancer, in 57 of which (46%) malignant cells were found in the sputum or bronchial secretion. Among 629 patients suffering from nonmalignant disease, there were 9 in whom the cytological test yielded an erroneous diagnosis (1.4%) of malignant disease. Five of these nine mistaken diagnoses were made in the first 200 patients examined and the other four among the some 700 patients examined at a later date. These figures suggest that the already low error rate of 1.4% could be further reduced by the experience gained by practice. The rate of correct diagnoses can be increased by repeating the test, but unfortunately even a trained cytologist needs about half an hour to complete a thorough scrutiny of the cells to be examined in a given case.

Dr. Iversen has also undertaken a study of 250 verified cases of bronchogenic cancer treated in his hospital between December, 1948, and July, 1952. In all these cases either the sputum or the bronchial secretion or both were examined cytologically. In 152 cases squamous cell carcinoma was diagnosed. The remaining 98 cases represented other forms of carcinoma. The cytological test was positive in 76 of the squamous cell cases (50%) and in 110 of the total of 250 cases (44%). Dr. Iversen concludes that the cytological test is of diagnostic value, a matter of great importance in operable cases of bronchogenic cancer.

Therapeutic Studies of Arterial Hypertension.—In several Danish hospitals much attention is being paid to the medical treatment of hypertension. At the Medical Department of the Frederiksborg County Central Hospital, Dr. Vagn Rønnov-Jessen and Dr. Viggo Bech have given an extensive trial of hexamethonium to 20 patients suffering from severe arterial hypertension. At first the drug was given orally in the form of the bitartrate of hexamethonium, 2 tablets of 0.25 gm. each being given three times daily, the dosage being gradually increased to 16 tablets daily. Only two of the eight patients treated in this way responded satisfactorily. The drug was next given subcutaneously as well as orally. A 10% solution of the bromide of hexamethonium was then given twice a day, the initial dose of 15 mg. being gradually increased by 5 to 10 mg. after every other injection. This increase of dosage was continued till each injection was followed by a suitable fall of blood pressure lasting a few hours. Of the 20 patients treated by this combined oral and parenteral mode of administration 2 discontinued treatment within three weeks and a third after three months. The remainder have continued this treatment for several months. Side-effects included severe constipation, from which nearly all the patients suffered at the beginning of the treatment. Giddiness due to a fall of the blood pressure usually passed off after a few weeks, partly because the dosage most suitable for each patient had been discovered by them; there was, however, one patient who discontinued the treatment after a fortnight on account of giddiness. In as many as 11 cases blurred vision and difficulties on reading were experienced, but they were transitory with only one exception. On account of these and other drawbacks to this treatment, it seems to be indicated only for patients seriously handicapped by hypertension. On the other hand, it is admitted that hexamethonium marks a significant epoch in the treatment of hypertension. Its administration should always be started in hospital where the suitable dosage can be established and the reactions to it closely controlled.

From the Medical Department of the Aarhus County Hospital comes a report by Dr. Poul Bechgaard and Dr. Leif Paulsen on tests they have carried out with Hydergine (methanesulfonates of dihydrogenated ergotoxine alkaloids) whose beneficial action on hypertension has recently been reported in Swiss and German publications. Among the 34 patients given parenteral injections of this drug were 14 who responded with a fall of blood pressure, while a slight effect was obtained in 12 and none in 8. As compared with hexamethonium, Hydergine would seem to be definitely less effective. In *Ugeskrift for Laeger* for April 16, 1953, which contains the reports referred to above, tables and graphs are given illustrating details of the tests to which the patients were subjected when treated in hospitals.

Births, Marriages, and Deaths.—A government report on movements of the population in 1951 shows what profound changes can take place in a comparatively short time with regard to such acts as marriages and divorces. For example, in the five year period 1941-1945 there were only 4,868 divorces yearly in Denmark. In the next five year period this figure had jumped to 7,084 yearly. In 1951 it was lower, with only 6,681, a figure corresponding to 18% of the marriages in the same year. The average duration of marriage before divorce was 10 years, but one-third of the divorces followed marriages of less than five years' duration. In the five year period 1925-1930 only 4.7% of the men and only 3.5% of the women marrying each year in this period were divorcees. The corresponding percentages in 1951 for men and women were 13 and 12, respectively. In this year the average age of hitherto unmarried persons at the time of marriage was 27 years for men and 24 years for women. As was to be expected, the men who married after the age of 60 greatly outnumbered the women marrying after this age (562 men to 166 women). In 1951 the number of mothers giving birth to twins was 1,008, and 10 gave birth to triplets. Up to 1948 the percentage of infants born from year to year out of wedlock was remarkably constant: 10%. In 1951, the number of illegitimate infants constituted only 7% of all the births.

Operations for Hemorrhoids Compared.—In the 16 year period 1935-1950 a total of 235 patients were operated on for hemorrhoids at the Bornholm County Hospital, Milligan's operation being performed in the first half of this period and the Jørgen-Jensen modification of Whitehead's operation in the second half. Recently Dr. Mogens Felbo and Dr. Ole Kofod, who are attached to this hospital, have succeeded in contacting 173 of these patients, 98 of whom underwent the modified Whitehead operation and 75 the Milligan operation. The percentage of patients expressing satisfaction with the operation was much the same for the two groups (82% Whitehead and 81% Milligan). But while 26% of the patients who underwent the Whitehead operation complained of postoperative rectal hemorrhage, only 17% of those having Milligan's operation did so. The Whitehead operation proved inferior to the Milligan technique also with regard to the recurrence or relapse rate, which was 14% for the former and only 8% for the latter.

The Late Professor Bock.—Johannes C. Bock, the father of experimental pharmacology in Denmark, was born in Copenhagen in 1867. After qualifying as a physician in 1893, he worked for two years at the Physiological Institute under

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The items in these letters are contributed by regular correspondents in the various foreign countries.

Prof. Christian Bohr, who did much to shape his subsequent career. At this institute he carried out studies on the physiology of respiration. After working in 1896 under Schmiedeberg at Strasbourg, Bock returned to Denmark where he studied at the University Pharmacological Institute in the period 1897-1900. He was only 33 years old when he was appointed professor of experimental pharmacology, and during the following decade he published a series of studies, many of which are still regarded as classics. In later years original research was, to a certain extent, set aside by the claims made on Bock as an administrator and organizer, and it was largely due to him that the school of dentistry, to which he was attached as a teacher, came to be reorganized. From 1907 to 1912 Bock was in charge of this school. In the period 1909-1939 he was adviser to the government in pharmacological problems, including forensic toxicology. Between the two world wars he undertook intensive research and educational studies of chemical warfare, and he did much to prepare the way for combating gas warfare. After his retirement as professor in 1938, Bock continued to live a very active life, and during the occupation of Denmark by the Germans he traveled widely, giving lectures on civil air defense. Painting and gardening were among his hobbies. In the summer of 1952 a motor car accident crippled him badly, and he was still suffering from its effects when he died early in 1953.

ITALY

Supracondylar Fractures of Humerus.—Professor Sanzone read a paper on supracondylar fractures of the humerus at the meeting of the Medical and Surgical Society of Taranto, Jan 27. Describing this specific type of inferior epiphyseal fracture of the humerus that is characteristic of infancy, he discussed the progressive phases of this ossification in infancy and puberty. Among the various anatomic elements that contribute to the causation of the fracture are the epitrochlear muscles, especially the round pronator.

The modern method of reduction aims almost systematically at the closed reduction. Great consideration should be given to the technique of stretching the epitrochlear muscles so that the distal fragment may accomplish its anatomic alinement. The radiological picture is very important for differentiation from other types of local fractures.

Professor Sanzone said that the sequela of Volkmann's paralysis should not be ascribed to the system of immobilization used but rather to failure in reduction of the fracture. In making the circular plaster bandage, it is advisable to open the anterior groove soon after its solidification, making the fixation rely on the back splint. Functional restoration depends mainly on early reduction.

In the discussion that followed, Professor De Rosa said that use of the plaster bandage is not devoid of dangers if the topography of the fracture is considered. Therefore, he believes it is wise to hold the reduction at first with a temporary bandage that can later be transformed into a permanent bandage. As for closed reduction, Professor Buonsanti favors the maneuver of flexion of the forearm with leverage on the wedge of Lorenz. This technique, which consists of traction and countertraction, can be performed without any assistance. In the distention of the muscles the forearm is bent as much as possible to insure the greatest possible contact between the stumps and the formation of bone spurs by the diaphysary stump is avoided. These spurs can cause imperfect function because of para-articular block. He also agreed on the necessity of early reduction of the fracture, since this is the only technique capable of assuring good results.

Medical and Surgical Society Meeting.—On Dec. 14, 1952, the medical and surgical society of the Romagna region held a meeting at which many papers were read.

Diaphragmatic Hernia.—Drs. Vazzocchi and Pezzani discussed diaphragmatic hernia. One case was presented, and the etiology, diagnosis, and therapy were discussed. Professor Sighinolfi said also that diaphragmatic hernia on the right side seems to be less common than on the left and that from his personal experience he could recall only one case with hernia on the right. This patient was a child in whom a segment of the transverse colon had herniated into the thoracic cavity through a narrow hole in the right side of the diaphragm and had afterward become strangulated and gangrenous. The young patient died. In addition to the correct differentiation of diaphragmatic hernias as fetal and embryonal, with and without a hernial sac, respectively, one must keep in mind the possibility of an eventration in which the diaphragmatic muscle is distended and relaxed and has atrophic fibers.

Carcinoma of Ampulla of Vater.—Drs. Bazzocchi and Pezzani discussed also a rare case of carcinoma of the ampulla of Vater in a 25-year-old man in whom the symptomatology had begun when he was 11 years old and who had a severe and obstinate form of icterus. The tumor was removed by the transduodenal approach and he has been clinically cured for many months.

Professor Sighinolfi, the chairman, intervened and, since the speakers had mentioned the finding of an obstructed gallbladder, he thought a note of comment was needed. He said that the failure of the gallbladder to fill up after oral administration of a contrast medium cannot be interpreted as indicating obstruction of the gallbladder. More reliable data may be obtained after administration, a few hours later, of twice as much contrast medium. X-ray examination of the gastrointestinal tract with accurate visualization of the duodenal loop is indispensable for a correct diagnosis. Dr. Jasonni believed that the distension of the gallbladder in the case under discussion should be considered an important element in the differential diagnosis; it could make one reject the calculous nature of the syndrome and suspect its neoplastic nature.

Fractures of Clavicle.—Professor Beluffi, from Pesaro, discussed open treatment of fractures of the clavicle. Since the closed methods of reduction and immobilization of the fractures of the clavicle are not well tolerated or give imperfect results and since, on the other hand, the modern methods of transskeletal traction require complex apparatus, he believes that in most cases of fracture of the clavicle open reduction should be used. The surgical treatment does not present technical difficulties nor dangers for the patient. It gives a perfect reduction in almost all cases. Moreover, it guarantees a solid and aesthetic callus with the best restoration of function. This method should be used not only in transverse fractures but also in oblique fractures where there is a third fragment. The fragment should never be removed but should be reduced to its proper place without damage to the muscle connections to avoid the danger of a pseudoarthrosis. The surgical technique should be individualized to the anatomic lesions of each case. In most cases the suture or cerclage with chromic surgical suture, nylon, or metal wire is sufficient. Fixation with Kirschner wire is indicated in some cases and is a good method; in some instances Professor Beluffi obtained favorable results with osteosynthesis with small pieces of vitallium.

In the discussion that followed, Professor Borellini agreed with Professor Beluffi that no closed orthopedic treatment gives a perfect reduction of some fractures of the clavicle. Among the closed methods the skeletal traction according to the technique of Filippi deserves special mention, since it gives good anatomic and functional results. As for open reduction, he believes that the best method is fixation by the retrograde intramedullary approach with Kirschner wire.

Professor Sighinolfi observed that most sequelae of fracture of the clavicle occur in patients treated by physicians working for accident insurance companies. As a rule, however, the residual deformities do not markedly affect function. In the reductions that he obtained by means of cerclage with a silver wire, there was sometimes delayed formation of bone callus; in other cases there was instead abundant callus formation. He obtained very good reductions with the apparatus that was proposed by Cornacchia.

Prostatectomy Techniques.—Interesting papers on the various methods of prostatectomy were read. Dr. Bucci discussed the indications for prostatectomy by Hryntschak's method, although he did not minimize the advantage of Millin's technique.

Professor Bazzocchi thought that the criticism against Millin's method that a suppuration of Retzius' space may occur is unsound, since by this route even an acute prostatic abscess can be checked. Nevertheless, the possibilities and the good results of the transvesical approach should not be underestimated.

Professor Babini reported that he had performed many prostatectomies according to Millin's method, but had now reverted to Freyer's one-stage method. The patients have recovered in almost the same length of time. He does not emphasize the danger of hemorrhage because he has never had an alarming case of hemorrhage, although he does not pack the cavity left by prostatectomy.

Professor Beluffi observed that for some time there has been an increasing criticism of retropubic extravesical prostatectomy by Millin's technique and a return to one-stage transvesical prostatectomy. The method proposed by Hryntschak and described by Bucci is a variant of this. He has never used it and therefore does not know its advantages, but for some time his former enthusiasm for Millin's method has been decreasing and he has restricted its use in favor of transvesical methods. Of these, he prefers the one described by Mingazzini.

Bronchial Tumors.—Professor Sighinolfi discussed some clinical and roentgenologic aspects of bronchial tumors. First, he reported some cases of pulmonary tumors, from which he showed serial roentgenograms that demonstrated their slow evolution. Two of the tumors deceived him because the initial radiological manifestations could have been interpreted as localized tuberculous processes. Three other cases were interesting because of a picture of atelectasis caused by the initial localization of the tumor in the main bronchi. In two cases the cancer was demonstrated directly by bronchography; in one case good results were obtained with early operation. In the third case, in which the roentgenograms indicated atelectasis of the lower lobe, bronchoscopy revealed a circumscribed mass that partially occluded the lumen of the bronchus of the lower lobe of the right lung and that was diagnosed as Jackson's adenoma. Diathermic coagulation of the lesion gave such good results that the patient's condition returned to normal.

The discussion confirmed the difficulty of a correct diagnosis, which is sometimes impossible. In view of the statistical data concerning the undoubted increase in the rate of pulmonary tumors, every effort should be made to obtain as soon as possible a correct diagnosis so that the latest surgical techniques may be used successfully.

MEXICO

Influenza Epidemic in Mexico.—The world-wide epidemic of influenza of 1919 included Mexico, where a great number of persons were affected. There was a high mortality rate and a high incidence of neurological complications of the mesoencephalic type. The epidemic was severer in certain geographic areas such as the state of Michoacán. Since then no true cases of influenza had been observed in Mexico until January of this year, when, concurrently with the European and North American epidemics, an outbreak occurred. The epidemic was concentrated mainly in the large cities such as Mexico City, Guadalajara, Puebla, Monterrey, San Luis Potosí, and León. Undoubtedly the incidence was highest in Mexico City, where at least a third of its 3 million inhabitants were affected.

In contrast to the 1919 epidemic, however, the 1953 outbreak was noted for its mildness. There were no deaths directly attributable to it, and hemorrhagic manifestations, which were very common in 1919, occurred infrequently, with epistaxis being observed in a few cases. Finally, another sign of the mildness of the epidemic was its short duration, since it had disappeared completely at the end of five weeks.

The Department of Public Health, in its hospitals and other medical attention centers, and the Seguro Social (Department of Social Security for Workers) put into practice every measure available to decrease the severity of the epidemic. Antibiotics were distributed free of charge to many patients with complications. The following recommendations were made: 1. Patients should be isolated during the acute period. 2. They must not resume ordinary activities until the danger of complications have disappeared. 3. Nose and throat exudates of the patients, as well as all objects contaminated by their excretions, should be disinfected. 4. Crowded places should be avoided as much as possible. 5. Concentration of patients in homes, hospitals, or other institutions, for medical care should be avoided, in order to prevent the appearance of complications, particularly pneumonia. 6. As a general recommendation, it is better for the patients to be under medical care with adequate nourishment.

Second Assembly of Universities.—The second assembly of Mexican universities took place last February, in the colonial city of Guanajuato. Twelve universities and 14 institutions of higher learning were represented, most of them by their rectors, presidents, or directors. The rector of the National University of Mexico was elected president of the assembly and the rector of the University of Guanajuato, which was the host institution, vice president. The following general decisions were made at the meeting: (*a*) Every candidate to the preparatory schools (which correspond to the last year of high school and to the first of college of the North American system) will be subjected to a preliminary (selective) examination, and admission will be granted only when the results meet certain requirements. (*b*) To date the program of the preparatory schools has varied according to the type of professional studies chosen by the student, which means that he has been compelled to choose his profession when he entered preparatory school. It was decided that there will be a single program for the preparatory schools that will be followed by all students, without regard to the professional studies they follow afterwards. (*c*) A preliminary proposal was made to extend the preparatory school course to three years, adding one year to the present curriculum. (*d*) To a certain extent the courses of the preparatory schools will also be unified. They will be of four types: (1) courses in the sciences and humanities; (2) courses in aesthetic culture; (3) training activities; and (4) nonacademic activities. There will also be some elective courses. Several commissions were formed to continue the study, on a permanent basis, of diverse problems that became evident in the course of the discussions and to prepare the agenda of the next assembly of universities.

Congress of Tuberculosis and Silicosis.—The Fifth National Congress of Tuberculosis and Silicosis was formally inaugurated on Jan. 25 in Guadalajara, at the auditorium of the medical school. The meeting, which was organized by the Sociedad Mexicana de Estudios sobre Tuberculosis y Enfermedades del Aparato Respiratorio (Mexican Society of Studies on Tuberculosis and Respiratory Diseases), was attended by more than 200 delegates from Mexico and other countries, including such distinguished international specialists as Drs. Maxwell Chamberlain, Oscar Auerbach, and Leo Eloezer.

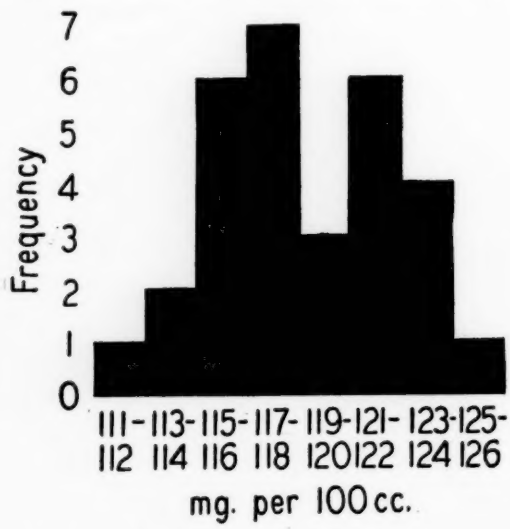
The inaugural lecture by Dr. Alfonso Aldama y Contreras was entitled "The Minimum Program for the Campaign Against Tuberculosis in Mexico." The following papers were read in the plenary sessions: "A Critical Evaluation of the Economic-Social Protection of the Tuberculous Patient in Our Country," by Dr. Ismael Cossío Villegas and colleagues; "Incidence of Silicosis in Mexico," by Dr. Ventura Aguirre of the Medical Department of the Secretary of Labor and Social Security; "A Study of Circulation in the Lungs in Silicosis," by Dr. Enrique Staines and co-workers; "Present Status of Surgical Treatment for Pulmonary Tuberculosis," by Dr. Alberto Ladrón de Guevara and co-workers; "Present Status of Medical Treatment for Pulmonary Tuberculosis," by Dr. Rodolfo Limón and co-workers; "Congenital Lung Diseases," by José Nava González; "Present Status of Cardiovascular Surgery in Mexico," by Dr. Clemente Robles; and "Cystic Lung Disease and Associated Pathological Changes," by Dr. Roberto Mendiola. Finally, Dr. Pedro Alegría, president of the meeting, insisted that the federal government should be responsible for every problem related to the campaign against tuberculosis in Mexico and suggested that special institutions be created for that purpose.

CORRESPONDENCE

ERRORS IN LABORATORY PROCEDURES

To the Editor:—Surveys of laboratory accuracy (Shuey, H. E., and Cebel, J.: *Bull. U. S. Army M. Dept.* **9**:799, 1949) have given adequate proof that too many laboratory reports are in such gross error that they are not only misleading but, at times, a cause of serious errors. It is not our purpose to delve into the whys and wherefores of such conditions but, rather, to discuss the fact that, assuming every laboratory procedure were perfectly performed, there would still be error. If this error were small enough to be unimportant in every instance then it would be of academic interest. Unfortunately, however, in many instances this error is larger than might be desired, because, through no fault of the laboratory, it is beyond reasonable control. This being the case it behooves the physician to gain at least a superficial understanding of the problems involved.

In measuring a discontinuous variable (the number of deaths occurring in a certain number of cases of smallpox), if it is assumed that the actual cause of death in each case was smallpox and that we can count correctly then there can be no error in measurement, for deaths can only occur in discrete intervals of 1, 2, 3, 4, ... Continuous variables, on the other hand, do not add values at discrete intervals but, rather,



can add an infinite number of values. The measurement of continuous variables is always subject to error; it is impossible to obtain an exact measurement of this type. It is impossible, therefore, to determine the exact value of a blood glucose level and, in this sense, all clinical laboratory procedures that measure continuous variables are in error. This error is relative and is important only when it becomes too large. For example, it is theoretically possible to measure a blood glucose level so accurately that it could be expressed as 100.345 mg. per 100 cc., with the knowledge that the last significant figure may be in error by as much as one unit. It is improbable that anyone would care very much about such accuracy. It would be of some concern to the physician, however, if he were told that a reported value of 100 mg. per 100 cc. might be off as much as 50 mg. per 100 cc.

It is important at this point to distinguish between the terms accuracy and precision as they are used in the modern statistical approach. A test is considered accurate if it gives a true result. For example, the Folin-Wu method of blood glucose determination is not very accurate, since a result of 100 mg. per 100 cc. contains approximately 20 mg. of reducing substances other than glucose per 100 cc. Certain other available methods are more accurate because most of the extraneous reducing substances are not measured. This does not mean, however, that a relatively inaccurate test is necessarily of no value to the clinician. The reducing substances other than glucose measured in the Folin-Wu glucose method fluctuate relatively little, and the physician merely becomes accustomed to interpreting the results in the light of a false normal range. Precision, on the other hand, is probably of greater importance. It is the degree of variation or reproducibility of results obtained by a method, such as the scatter of results if many aliquots of one unknown are tested. The less the variation the greater the precision is said to be. Accuracy and precision are completely independent of each other.

As an example of the variation of results obtained when a test is repeated on the same sample, the figure shows the distribution of the results of 30 analyses for blood sugar on a pooled blood sample, run by the Folin-Wu method.

The average of the results is 118.6 mg. per 100 cc. and is the best estimate available of the correct value for the method used. It is possible, by relatively simple statistical analysis, to determine limits on each side of this average that would include approximately 95% of all determinations made by the same laboratory on the particular unknown sample. These limits also represent an index of the precision of the method and can be expressed in terms of mg. per 100 cc. or in terms of per cent of the answer itself. In the example above, it was found that the precision of the Folin-Wu method at 120 mg. per 100 cc. was approximately ±10 mg. per 100 cc., or ±8.2%. It should be noted that these limits would encompass the correct answer in only approximately 95% of cases and, therefore, that one correct answer in 20 might fall outside these limits. A report of a blood glucose level of 106 mg. per 100 cc. does not mean that the exact level is actually 106; in fact, the probability is that it is not 106. What it does mean is that the correct answer for the method used is probably (95% confidence) within 10 mg. of the reported figure.

The same situation exists in all clinical chemical analyses. Ideally, all reports should be given with an indication of the error associated with them. Perhaps this would be rather impractical in clinical medicine, although this procedure is gaining favor, but it is important that physicians think in these terms. Error is critically important to the physician only when it becomes too large. The control of error within clinically permissible limits is the responsibility of the laboratory. This is not always a simple task. In most chemical tests an error of ±10% is not critical, but certain exceptions exist. It is difficult, for example, to perform a calcium determination on serum by most of the procedures in use with an error less than ±5%. This means that the true value of a reported result of 9 mg. per 100 cc. may lie anywhere between 8.5 and 9.5 mg. per 100 cc. This is not the fault of the laboratory.

There are a number of factors that contribute to this unavoidable error. Every step in a chemical procedure cannot be reproduced exactly and contributes its share of error to the total, over-all error of the test. For example, among the sources of error in the Folin-Wu glucose determination are measuring the blood, measuring the reagents used in preparing the protein-free filtrate, measuring the protein-free filtrate, the copper reduction step, reading the color density, and the variation of the reagent blank (Henry, R. J., and others: *Am. J. Clin Path.* **23**:285, 1953). It is true that the over-all error can be reduced by more exacting technique in one or more of these steps. Reduction of the error at one or two steps, however, has relatively little effect on the over-all error. To reduce materially the error at all steps would involve considerably more work, which would increase the cost of the test to the patient. Actually, there would be little point in reducing error of a test that is already sufficiently precise for clinical purposes. In certain cases, however, in which greater precision is desirable, it is impractical or impossible at the present time to accomplish this.

In the field of hematology, the unavoidable errors are not sufficiently appreciated. A physician receives a report on an erythrocyte count of 3,800,000, places the patient on iron therapy, repeats the count a week later, and receives a report

of 3,400,000. At this point, the laboratory is apt to be blamed for poor work. Actually, the laboratory may well be correct in both counts, and, yet, the true counts may have been 3,400,000 and 3,800,000 respectively. The reason for this is that, if one follows the accepted technique of counting five 0.04 mm. squares of a hemocytometer filled from one diluting pipette, the maximum unavoidable error in counting is ±18% (Berkson, J.; Magath, R. B., and Hurn, M.: *Am. J. Physiol.* **128**:304, 1940). A report of 3,800,000 erythrocytes per cubic millimeter of blood is not an actual count of cells in a cubic millimeter but a calculation based on a count of relatively few cells. This error is termed unavoidable since it is the error assuming no error in technique. The true count, in the instance in which 3,800,000 erythrocytes are reported, is probably between 3,100,000 and 4,500,000.

Nearly every procedure performed in the clinical laboratory could be discussed from the standpoint of unavoidable or permissible error. Our purpose is to call this type of error to the attention of the clinician so that he can interpret laboratory reports more intelligently.

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TRANSVESTISM

To the Editor:—The issue of May 30, 1953, of THE JOURNAL (**153**:391, 1953) contains an article on the surgical treatment of transvestism by Hamburger and associates. The Danish authors describe the case of a male transvestite who considered himself, like many transvestites, "the victim of a cruel mistake," namely of being a female in a male body. The patient demanded a removal of the hated male organs, since otherwise life was not worth living and he would commit suicide. After prolonged, but psychiatrically not quite satisfactory examinations, the patient was castrated in three stages: (1) hormonal castration with estrogenic hormones, (2) orchidectomy, (3) amputation of the penis, implantation of the urethra into the perineum, and creation of labia-like structures by plastic surgery of the scrotum.

Although the authors state that "it cannot be denied that conism (transvestism) may be psychically conditioned," they proceeded with the surgical treatment and based this course of action on hypotheses of genetic (chromosomal) changes that allegedly create sex intergrades and are responsible for the psychic striving of the transvestite to be identified with and regarded as a woman.

Nothing in the preliminary physical and hormonal examination of this patient offers any convincing evidence that somatic, genetically determined factors played a predominant role in this case. The young man had testes "somewhat under average size but of normal consistency." Secondary sexual characteristics were male. "He was of the asthenic type with a feminine habitus." There are men of exactly the same "habitus" who do not show any sexual deviation and conversely many sexual deviates whose body type is fully masculine. It is not understandable how genetic, chromosomal changes would affect a person's psychic structure and emotional attitudes without any somatic changes of an "intergrade" nature. The acceptance of effeminate attitudes and mannerisms by some homosexuals and transvestites can be very well explained by the strong psychic drive to identify with a woman. How would we explain the presence of sexual deviation in men who neither in their body build nor in their behavior show the faintest trace of "intergrade" characteristics?

I do not wish to deny the presence of constitutional, hereditary factors in mental illness and in sexual perversions; however, we cannot assume that a specific genotype will produce a specific perversion such as homosexuality, fetishism, or transvestism. Psychiatric histories of sexual deviates show certain environmental factors that interfered with their normal psychosexual development and led to a specific perversion.

The psychiatric history of the patient as published in THE JOURNAL is very brief, and the patient's statements that he never felt "any deep affection" for his sister and that he had no "exceptional feelings" for his parents are taken at face value. No attempts were made to elicit forgotten childhood memories with sodium amobarbital (Amytal) interviews or even to use projective psychological tests (e. g., Rorschach and Thematic Apperception Tests). These techniques would have shown much more than the patient was able to disclose in ordinary psychiatric interviews. From the history as given it seems this patient grew up in a vacuum. A deeper going psychiatric investigation, even without resorting to psychoanalysis, would have disclosed psychological and emotional factors that determined this patient's deviation from the normal psychosexual development. Contrary to the statement of Hamburger and associates, patients with transvestism were psychoanalyzed and a report of a case was published by Fenichel (The Psychology of Transvestism, *Internat. J. Psycho-Analysis* **11**:211, 1930). It is true that reports on the treatment of transvestites are scarce in the psychoanalytic and psychiatric literature. This is due to the extreme reluctance of transvestites as well as of other sexual deviates to undergo any treatment that actually would remove the perversion and deprive them of their perverse gratifications. The difficulty of getting the patient itno psychiatric treatment should not lead us to compliance with the patient's demands, which are based on his sexual perversion.

Transvestites present the picture of an especially complex sexual deviation and show features of fetishism (overevaluation of female clothing), homosexuality (desire to be a woman), exhibitionism (desire to show themselves as a woman), and masochism. The patient reported on by the authors showed marked masochistic traits, as exemplified in his persistent demand to be castrated (a comparable observation was published by M. Grotjahn [Transvestite Fantasy Expressed in a Drawing, *Psychoanalyt. Quart.* **17**:340, 1948]). We observe this as a symptom in some schizophrenics who at times will resort to self-mutilation, be it self-castration, self-blinding, or some other form of serious self-inflicted injury. It would not be surprising if a closer investigation of this patient were to disclose the presence of an underlying schizophrenic process that has not become manifest in any other overt symptoms except for the insistent striving to be castrated. With all due respect for the surgical skill of Dr. Hamburger and his associates, one can hardly maintain that the psychiatric indication for this procedure was sound.

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CHILDREN'S SHOES

To the Editor:—Relative to the article "Children's Shoes" by Louis Starr in THE JOURNAL (**151**:1401 [April 18] 1953), I would like to make the following comment. So far as the normal foot is concerned, either adult's or child's, the shoe is essentially a platform designed to protect the foot and to keep it off the ground. Although custom and style have determined certain changes, no shoe can be too large to fit properly. This, of course, becomes ridiculous if carried to the extreme, but the point is only a shoe that is small or that cramps or puts undue pressure on tender structures can fit poorly. As long as a youngster can wear his shoes easily and without tenderness at pressure points, his shoes fit. Persons with normal feet are comfortable in practically any shoe so long as it is large enough; those accustomed to tight-fitting and poorly-designed shoes complain, initially, that adequate shoes "flop" but, after several weeks, become accustomed to the freedom of motion of the larger shoe. A large shoe is out of the question for women who wear high heels, since tightness of the shoe is necessary to keep the foot from sliding forward.

I think the normal child may be permitted to go barefoot as long as he does not endanger himself. I see no objection to healthy youngsters going barefoot but I do agree that youngsters in the house should not be permitted to wear slippers or to go barefoot during convalescence.

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MEDICAL LITERATURE ABSTRACTS

UNITED STATES

American Journal of Public Health, New York

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Iliac Bone Grafts Replacing Tantalum Plates for Gunshot Wounds of Skull. C. L. Kiehn and A. Grino.—p. 395.

Simultaneous Traumatic Dislocation of Hip.—In an automobile collision a 38-year-old man sustained multiple wounds and abrasions, a posterior dislocation of the left hip, with small fractures of the posterior superior acetabular edge, and an anterior dislocation of the right hip with less extensive acetabular rim fracture. Three unsuccessful attempts with the patient under general anesthetic, with the help of four assistants, were made to reduce the right hip by traction and manipulation. The head of the femur could be brought to the acetabular edge but not slipped into the joint. For the fourth attempt the patient was lowered on to the covered floor and there a reduction was accomplished. Because of falling blood pressure and shock, reduction efforts on the left hip were postponed. A plaster of paris hip spica cast was applied, covering the right leg completely and the left leg (hip still dislocated) to the knee. This was to maintain the reduction of the right hip and to hold the left hip in status quo. Eleven days after the accident the plaster encasement was removed. Under general anesthesia, with every care not to rotate or flex the right thigh, he was again placed on the covered floor. The posterior dislocation of the left hip was reduced by gentle but strong traction applied in the long axis of the leg, with counterpull and pressure on torso and pelvis, and followed by slow flexion and internal rotation of the left leg and thigh, accompanied by pushing-up pressure on the greater trochanter of the femur. The patient was encased in a double body plaster of paris spica covering both legs, held in partial abduction and slightly flexed at the hip joints. Six weeks later this cast was removed. Two weeks after that the patient had good locomotion and only a slightly diminished tractile sensation on the outer side of the left foot. Necrosis of the caput femoris did not follow this instance of simultaneous traumatic dislocation of both hips. Fractures of the acetabular rims healed with no apparent blocking of hip joint motions up to six years after dislocation. When shock exists, with bilateral dislocation of the hip, one side may be reduced at a time, without too great an interval (10 days). Putting the patient in a position where one may apply one's utmost physical power under control is the wisest course in reducing dislocation of the hip. The floor can be used. Prolonged rest after reduction of hip dislocation with slowly increasing active motions of the hip and long delayed weight-bearing favor a good prognosis.

Annals of Allergy, Minneapolis

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Small Dosage Injectable Antihistamine (Chlor-Trimeton Maleate Injectable) in Treatment of Allergic Diseases: Clinical Study. C. M. Jenkins.—p. 96.

Exacerbation of Ivy Dermatitis by Rhus Antigen Injections.—The histories of four patients in whom exfoliative dermatitis developed following the injection of rhus antigen for ivy poisoning are presented. In all four cases the dermatitis apparently began as simple ivy dermatitis and grew steadily worse with each injection of the rhus antigen, or else additional sensitivity appeared either in the form of exfoliative dermatitis or pompholyx or both. Reyer hopes that as more instances of these and other complications of this rather illogical form of poison ivy treatment are brought before the practitioners, this type of antigen injection will be stopped and more beneficial methods developed. Thirty years ago several papers appeared praising the use of rhus antigen by injection in treating acute ivy poisoning; however, reports gradually appeared that showed a lack of benefit or even harm from the use of the injected antigen during the attack. Contradictory reports about the efficacy of rhus antigen injections led to an investigation of the results obtained with this treatment. The conclusions

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Titles marked with an asterisk (*) are abstracted.

were that since no satisfactory evidence yet shows the course of ivy dermatitis to be improved by such injections, since many patients have been shown to be made worse by such treatment, and since the practice is not in accord with immunological principles, the use of the rhus antigen in the treatment of the acute phase of the disease should be discouraged.

Annals of Internal Medicine, Lancaster, Pa.

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*Immunologic Mechanisms in Idiopathic and Neonatal Thrombocytopenic Purpura. W. J. Harrington, C. C. Sprague, V. Minnich and others. —p. 433.

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Some Observations on Postgraduate Medical Education. R. M. Becker. —p. 568.

Immunologic Mechanisms in Thrombocytopenic Purpura.—Tests performed on 35 patients between the ages of 2 and 71 with idiopathic thrombocytopenic purpura indicated that an immunologic mechanism is responsible for the low platelet count in many of these cases. Platelet agglutinins were demonstrated in vitro in the plasma of many of these patients, and a factor presumably identical to this platelet agglutinin proved capable of inducing thrombocytopenic purpura and altering megakaryocytes in normal subjects or patients with inoperable cancer who were transfused with 500 cc. of whole blood or its plasma equivalent obtained from 26 patients with thrombocytopenic purpura. Splenectomy was performed in 28 of these patients, and 19 were treated with cortisone or corticotropin (ACTH). Remission following splenectomy was not necessarily accompanied by disappearance of the thrombocytopenic factor from the patient's plasma, but this factor did disappear in spontaneous remissions and in those induced by corticotropin or cortisone. Of 14 patients in whom evidence for increased platelet destruction was lacking, 11 were treated by splenectomy. Only one had a good response, and two were briefly benefited. It is suggested that idiopathic thrombocytopenic purpura may also arise from failure of megakaryocytes to produce circulating platelets. Reference was made to the existence of serologically different platelet types. A study was made of seven women who had had a total of 12 pregnancies in which either the mothers or the infants had purpura. Three of the mothers had platelet agglutinins in their plasma; all eight infants born to these three mothers had thrombocytopenic purpura and it is postulated that neonatal thrombocytopenia in these infants developed as a result of transmission across the placenta of maternal autoagglutinins for platelets. Two of the seven mothers were in apparently perfect state of health but gave birth to infants with thrombocytopenic purpura; isoagglutinins in the maternal serum for the infant's platelets were demonstrated in one case. It is suggested that neonatal thrombocytopenia was due to development of isoagglutinins because of fetal and maternal platelet incompatibilities. The remaining two mothers had severe thrombocytopenic purpura at the time of delivery, but had no platelet agglutinins in their plasma. The infants in both instances were normal. These two cases are considered to represent examples of maternal thombocytopenia in which platelet agglutinins have played no part in pathogenesis, and consequently the infants' platelets were normal.

Cardiac Catheterization.—Venous catheterization of the right side of the heart and of the pulmonary artery according to Cournand and Ranges' technique was performed in 128 patients with heart disease with various etiological bases. Of these 128 patients, 15 adults are described in detail in whom cardiac catheterization was employed in diagnosis and management and found to be practical. As a result of his experience the author states that cardiac catheterization was most helpful in the diagnosis of left-to-right shunts, such as patent ductus arteriosus, atrial septal defect, and ventricular septal defect. By means of hydraulic formulas, catheterization may aid in estimation of the degree of stenosis of various valves, e. g., pulmonary, mitral and tricuspid valves. In the author's hands, the hydraulic formulas have not been satisfactory in estimating the size of the patent ductus arteriosus. By means of pressure curves in the right atrium and pulmonary "capillary" pressure curves, the catheter may be of value in the diagnosis of the insufficiency of the tricuspid and mitral valves. The procedure may aid in the diagnosis of right ventricular failure by showing elevated pressure of the right ventricle at the end of the diastole and elevated right atrial mean pressure. The catheter may aid in the diagnosis of left ventricular failure by showing elevation of the pulmonary "capillary" mean pressure and widening of the arteriovenous oxygen difference, if the failure is of the low output type. The catheter may aid in the diagnosis of high output failure, e. g., in thyrotoxicosis, beriberi, systemic arteriovenous fistula, anemia, and Paget's disease of the bone. By means of characteristic right ventricular pressure curves the catheter may be helpful in the diagnosis of pericardial constriction and cardiac tamponade. Catheterization aids in the diagnosis of cor pulmonale in showing high pulmonary arterial pressure associated with normal pulmonary "capillary" pressure and a tendency toward normal cardiac output. Pulmonary artery pressure may be expected to rise after digitalization in cor pulmonale with failure, and to fall after digitalization in left ventricular failure. By means of the determination of the oxygen saturation of the pulmonary "capillary" blood, catheterization may be used to differentiate between arterial oxygen unsaturation due to emphysema and that due to right-to-left shunt.

Reiter's Syndrome.—Of 23 men between the ages of 21 and 41 years with Reiter's syndrome, 20 had urethritis, conjunctivitis, and arthritis, while the other 3 showed little evidence of either urethritis or conjunctivitis but did have arthritis and typical mucocutaneous lesions that were present in all 23 patients. Several small, erythematous papules often surmounted by a vesicle were observed on the prepuce and/or the glans penis in 18 of the 23 patients. After rupture of the vesicle, the ulcerated papule was covered by a purulent crust or a cornified layer. Occasionally erosion of the urethral meatus was present. An erythematous, weeping, eczematoid eruption of the scrotum and groin was seen in four patients. Vesicles surrounded by a zone of erythema, which soon ruptured leaving small ulcers, were observed on the palate or buccal mucosa in 11 patients. Five patients showed changes in fingernails and five in toenails; subungual hemorrhages, splitting of the nails into several opaque layers, and conversion of nails into thick, horny appendages were observed. Five patients had dermal lesions morphologically indistinguishable from those of keratodermia blennorrhagica, involving the genitalia, groins, perineum, buttocks, extensor surface of legs, knees, elbows, soles of the feet, axillas, and scalp. Vesicular and papular lesions in the skin and mucous membranes were so common in the authors' series as to aid in the diagnosis of doubtful cases. The arthritis was prolonged in duration but rarely produced permanent deformity. Fourteen patients admitted a recent extramarital sexual experience before the onset of their disease. One patient was observed during two episodes of Reiter's syndrome, the second episode beginning six months after cessation of the first. In each instance this patient admitted extramarital sexual experience with the same woman about one week before the onset of his disease. In 14 of the 23 patients, the first symptom was urethritis. These data suggest that the disease may be due to a venereal infection, with the urethra as the portal of entry. Bacteriological and serologic studies demonstrated active gonococcal infection in only one of the 23 patients. Pleuropneumonia-like organisms were isolated from the urethral exudate in only one of the eight patients examined. Fecal cultures in five patients with diarrhea failed to show Shigella or other bacterial pathogens. The cause of Reiter's syndrome

remains in doubt. The most effective therapeutic measures were rest, high-caloric diets, salicylates for pain, and intensive physical therapy. Streptomycin seemed to produce slight improvement in four of six patients. Cortisone and corticotropin (ACTH) caused a temporary decrease in fever and arthritis of a few patients.

California Medicine, San Francisco

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*Multiple Arsenical Cancers of Skin and Internal Organs. S. C. Sommers and R. G. McManus.—p. 347.
Incidence of Multiple Cancer. T. A. Watson.—p. 365.

Trauma as a Cocarcinogen in an Oil Worker.—The 60-year-old man whose case is presented had been employed by a petroleum corporation for 30 years. His work involved frequent skin contamination by a moderately heavy refined oil used in transformers and electrical motors. Physical examination revealed a tumor mass, 1.7 cm. in diameter, extending 3 to 4 mm. above the skin surface over the dorsum of the third right metacarpal. One month before, the patient had cut the dorsum of his right hand at the site of the present tumor. The wound healed slowly, and working resulted in minor abrasions to the overlying eschar. Two weeks prior to entry, a severe blow was received on the injury site, and following this the tumor appeared and grew rapidly. It was removed by excision, and microscopic examination revealed a grade 1 squamous cell carcinoma. The concept of "sensitization" or "preparation" of skin by means of suboptimal exposure to carcinogenic hydrocarbons has been experimentally established by several investigators. The suboptimal exposure converts some of the cells in the skin of experimental animals to a preneoplastic condition. Following this stage, nonspecific agents such as wound healing, freezing with carbon dioxide snow, croton oil, and mechanical irritation convert the process to true neoplasia. In this patient occupational exposure to petroleum products presumably served as the initiating mechanism, and the wound healing following trauma as the promoting agent.

Aureomycin and Nitrogen Mustard in Human Cancer.—Regional intra-arterial administration of the nitrogen mustard (methylbis[2-chlorethyl] amine hydrochloride) has been found to produce on certain cancers therapeutic effects that could not be achieved by intravenous administration. Serious systemic infection occurred, however, in several patients who were given daily doses of the nitrogen mustard through an indwelling arterial cannula. The source of infection in these cases was either the arterial cannula tract or the devitalized tumor tissue. To prevent such systemic infection, prophylactic use of a broad-spectrum antibiotic such as aureomycin was considered desirable. The indwelling cannula offered a safe route of administration of aureomycin hydrochloride buffered with sodium glycinate (buffered aureomycin). Furthermore, reports that high concentrations of aureomycin affected rapidly dividing cells in tissue culture, in plants, and in animal tumors suggested that this drug might also be a chemotherapeutic agent active against cancer. This was further supported by the observation that simultaneous exposure of cells in tissue culture to nitrogen mustard and buffered aureomycin was more cytotoxic than exposure to the same concentration of either drug alone. For these reasons, nitrogen mustard and buffered aureomycin were administered intra-arterially to 17 patients with hopeless cancer. The tumors regressed enough to permit surgical excision in four patients previously considered inoperable; one refused operation.

Multiple Arsenical Cancers of Skin and Internal Organs.—Sommers and McManus review 27 cases of arsenical cancer in 19 men and 8 women. Twelve had been treated for psoriasis with Fowler's (potassium arsenite) solution; one had received injections of arsenicals because of syphilis; two had had occupational exposure to arsenical sprays; and in four others occupational exposure seemed possible. Seven had been treated with arsenic for swollen lymph nodes, burns, dermatitis, or chorea. In three, the form of exposure was unknown. The arsenical origin was recognized clinically in all except one of the cases by the characteristic multiple keratoses of palms and soles. In addition to the large number and extent of multiple skin cancers, four of the six patients who came to autopsy had additional internal cancers, three at multiple sites. These visceral lesions were in the bladder, prostate, esophagus, colon, kidney, and chest wall. In five other patients who died, death was ascribed to cancer of the tonsil, esophagus, breast, pancreas, and lung. One patient with multiple skin cancers and lung cancer is living. Some skin lesions apparently developed from the epidermis, sweat, or sebaceous glands, and possibly hair follicles. Gradations of epidermal atrophy, hyperplasia, precancerous changes, carcinoma in situ (Bowen's disease), and invasive cancers were observed. The visceral cancers suggest that a second predisposed tissue is the squamous epithelium of the mouth and esophagus and the metaplastic squamous epithelium of the respiratory tract. The third region of predilection is the urogenital epithelium of the kidney, ureter, and urinary bladder. Heredity, chronic irritation, local sensitivity, and endocrine abnormalities may favor arsenical carcinogenesis. Present knowledge of the biochemical effects of arsenic suggest that it influences hydrogen transport, nucleoprotein metabolism, and phosphorylation. It acts mainly on the nucleus and interferes with mitosis. The consequences are visible cytologically as disturbed epithelial growth and delayed maturation, particularly in epidermal nuclei. Mechanical stimuli, roentgen rays, and hormonal imbalances may have additional carcinogenic effects.

Cancer Research, Chicago

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Influence of 8-Azaguanine on Mitotic Rate and Histological Appearance of Certain Normal and Neoplastic Tissues. G. L. Woodside, G. W. Kidder, V. C. Dewey and R. E. Parks Jr.—p. 289.
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Quantitative Relationship Between Thyroid Function and Growth of Pituitary Tumors Secreting TSH. J. Furth, W. T. Burnett Jr. and E. L. Gadsden.—p. 298.

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Negative Data from Experimental Cancer Chemotherapy Studies. Edited by C. C. Stock.—p. 1-200.

Critical Evaluation of Chemotherapy of Cancer.—In summarizing the present status of the chemotherapy of cancer, Gellhorn classifies the substances used according to their mode of action into three groups: (1) those producing an unfavorable environment for the cancer cell; (2) those modifying the systemic intoxication produced by cancer; and (3) those that damage the cellular functions. With the exception of the hormones, the chemical compounds that are used have significant toxicity for normal as well as for neoplastic cells. This precludes curative therapy, since the treatment necessary for destruction of the tumor would be lethal to the host also. Another limitation is the small number of tumor types that respond to drugs. Urethane, the folic acid antagonists, cortisone, and the nitrogen mustards play a role in the treatment of the malignant lymphomas and leukemias, which constitute only a small fraction of all the malignant neoplastic diseases. The empirical approach has largely consisted of screening chemical compounds for their effect on the growth of transplantable tumors in mice, rats, and rabbits. It must be recognized, however, that, with the possible exception of mouse leukemia, there is no evidence to demonstrate that transplantable or spontaneous tumors in laboratory animals are biologically directly comparable to human tumors. One apparent discrepancy between experimental and human tumors is in their relative growth rates. The cells of experimental tumors divide rapidly, and at any instant the majority of them are in an active phase of division. Human epithelial tumors grow relatively slowly, and morphological evidence indicates that only a small fraction of the cells are in active mitosis at one time. Since it is likely that cancer chemotherapeutic agents, like antibacterial drugs, can only destroy cells that are susceptible by virtue of active metabolism and division, it follows that effective drugs against human epithelial tumors will have to be administered and tolerated for long periods by the normal host cells. It may be significant that the drugs that are active in the currently employed animal tumor screening tests are effective principally against the most rapidly growing human tumors, the lymphomas and leukemias. The question is whether the screening techniques are missing compounds that are potentially useful against other tumors. The author suggests that more subtle end points than the ones now in use might indicate chemical compounds, that although they fail to produce dramatic changes in tumor growth after brief administration, might modify the growth of tumors when given over long periods.

Circulation, New York

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Management of Shock in Acute Myocardial Infarction.—Approximately half the patients with severe shock complicating myocardial infarction can be saved by active therapy with vasopressor drugs, blood, and plasma. The duration of shock without treatment is an important diagnostic criterion, because recovery is extremely rare when profound circulatory failure has persisted for a number of hours. Irreversible myocardial lesions are sustained when the injured myocardium undergoes a period of greatly reduced blood flow. Therapy designed to maintain the circulation at a level compatible with life will limit or prevent progressive myocardial deterioration and will enable a heart that is capable of recovery to resume adequate functioning. Thirty-two patients whose shock was so profound at the beginning of treatment that no hope of survival was justified were given active therapy with a combination of blood, plasma, and a vasopressor drug; 14 recovered, indicating that, however severe their shock, patients with acute myocardial infarction have a chance for life. The longer the patient remains alive under treatment, the greater his chances of recovery become. Some of the patients in this series recovered after long periods of deep shock; one did not definitely emerge from shock until the end of 48 hours of treatment. Pulmonary edema is a particularly unfavorable complication; experience in this series indicates that the best results when pulmonary edema is present are obtained by combating the shock. The four patients with this complication who survived received no therapy directed toward the edema other than small doses of morphine, but they showed impressive clearing of the lungs as the blood pressure rose and they emerged from shock. Clinical recovery from circulatory failure in the 14 survivors was associated with attainment of a pulse pressure of at least 25 mm. Hg. Treatment should be continued under the close attention of physicians until the emergency is over; nurses cannot be given the responsibility of making the many decisions required by the fluctuating condition of the patient.

Dibucaine Hydrochloride and Phenobarbital Sodium in Ventricular Tachycardia.—Dibucaine (Nupercaine) hydrochloride was administered intravenously by slow injection or constant venoclysis to 22 dogs with ventricular tachycardia accompanying myocardial infarction. The dogs were divided into four groups. Group 1 received dibucaine alone. Group 2 received dibucaine in addition to 3 or 5 mg. of morphine per

kilogram of body weight. Group 3 received phenobarbital sodium, 25 or 40 mg. per kilogram, as well as dibucaine. Group 4 received dibucaine in addition to pentobarbital sodium, 10 or 15 mg. per kilogram. Dibucaine alone was effective in suppressing ectopic activity, but vomiting and convulsive movements commonly occurred and interfered with administration in some animals. Administration of morphine before dibucaine was given prevented vomiting but did not prevent convulsive movements, and the ectopic impulse suppressor action was neither enhanced nor prolonged. Vomiting was also eliminated when phenobarbital was given before dibucaine, and only mild stretching movements of doubtful cause occurred in two of nine dogs during the tests. Phenobarbital enhanced and greatly prolonged the ectopic impulse suppressor effect of the dibucaine. Pentobarbital sodium eliminated vomiting and convulsive movements and enhanced the ectopic impulse suppressor effect of dibucaine without prolonging it. The blood pressure tended to rise or to remain constant in all slow administration tests, and there were only minor alterations in the P-R and QRS intervals in the electrocardiogram; rapid administration produced periods of prolonged QRS deflections and hypotension. Discontinuance of rapid infusion was followed by a return of all signs to normal within 30 seconds. There were no deaths in any of the groups. A combination of phenobarbital and dibucaine is regarded as an effective and relatively safe treatment for ventricular tachycardia accompanying myocardial infarction when suitable precautions are observed.

GP (J. Am. Acad. Gen. Practice), Kansas City, Mo.

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Journal of International College of Surgeons, Chicago

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Distribution and in Vivo Rate of Metabolism of Thiopental. F. E. Shideman, T. C. Gould, W. D. Winters and others.—p. 368.
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Hyaline Membrane Formation in the Newborn: Hematogenic Shock as Possible Etiologic Factor. D. B. Landau.—p. 183.
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*Banthine Therapy for Enuresis. J. F. O'Malley and R. H. Owens.—p. 188.
Surgical Management of Hypersplenism. R. M. Zollinger.—p. 193.
Pneumothorax Complicating Pneumoperitoneum Therapy: Report of Case with Associated Pleural and Peritoneal Effusion. J. T. Lawton.—p. 199.

Methantheline (Banthine) Therapy of Enuresis.—After defining enuresis as repeated involuntary micturition after the age of 3, O'Malley and Owens review the neurophysiology of the bladder in order to show the rationale of methantheline (Banthine) therapy. It has been demonstrated that methantheline suppresses the pelvic nerve stimulation of the bladder. For this reason methantheline has been used to treat irritable bladders, cystitis, and interstitial cystitis with ulceration (Hunner's ulcer). Since it is believed that the bladder of the enuretic patient is irritable, with a tendency toward uninhibited contractions, the authors decided to use methantheline to treat enuresis. By inhibition of the local reflex with methantheline, the bladder will gain more capacity and accommodate a larger volume without an increase in intravesical pressure. In this way, in spite of poor cerebral inhibition, adequate inhibition will be maintained at the reflex level. Two cases of enuresis treated with methantheline are reported in detail and nine more are charted. The ages of the patients ranged from 5 to 15. Methantheline was given at bed time. In one patient 25 mg. produced no significant improvement, but 50 mg. was temporarily effective. After a relapse, 75 mg. was given and the symptoms subsided. In the second patient 50 mg. of methan-

theline with phenobarbital and limitation of fluids for one hour before bed time produced immediate relief of enuresis. Relapse occurred in only 3 of the 11 patients, and by increase of the dose, the enuresis was overcome and continence was maintained.

Neurology, Minneapolis

3:239-320 (April) 1953

Pathologic Changes in Brain in Coma Following Ether Anesthesia. J. Denst.—p. 239.
Preliminary Studies of Sludged Blood in Multiple Sclerosis. L. Roizin, R. C. Abell and J. Winn.—p. 250.
Role of Pallidum in Genesis of Some Choreic Movements. E. A. Spiegel and H. T. Wycis.—p. 261.
Central Nervous System in Thrombotic Thrombocytopenic Purpura. H. A. Ludwig.—p. 267.
*Cerebral Complications of Serum Sickness. A. M. Park and J. C. Richardson.—p. 277.
*Sensitivity of Myasthenia Gravis Patients to Tubocurarine and Decamethonium. E. W. Pelikan, J. E. Tether and K. R. Unna.—p. 284.
Occurrence of "Continuous Symptoms" in Epilepsy Patients. J. S. Scott and R. L. Masland.—p. 297.
*Effect of Tensilon in Myasthenia Gravis. M. R. Westerberg, K. R. Magee and F. E. Shideman.—p. 302.

Cerebral Complications of Serum Sickness.—Two types of central nervous system involvement occur in serum sickness, peripheral and central. The entity referred to as serum neuritis is the commonest peripheral lesion. Isolated lesions of the cranial nerves have been described. A more generalized polyneuritis, which resembles that of acute infectious polyneuritis or the Guillain-Barré syndrome, and even acute ascending paralysis of the Landry type also may be seen with serum sickness. No instances of purely spinal lesions with paraplegic signs are on record, although in some cases of generalized polyneuritis accompanying serum sickness, pyramidal tract signs and sensory disturbance corresponding with a definite spinal level suggested the presence of some lesion of the spinal cord. The frequency of cerebral injury in serum sickness is difficult to know. After describing a case of Windorfer's "neuroallergic encephalitis," the authors say that the rarest manifestation of nervous system damage in serum sickness is focal cerebral injury. Two patients observed in the past year with focal brain damage following injection of serum are described. The first patient became very drowsy seven days after receiving antitetanus serum and on the eighth day awoke with an urticarial eruption over the face, arms, and trunk. A few hours later, he suddenly became unconscious and was semicomatose over the next 48 hours. On the 11th day after injection he regained consciousness, but had a complete right hemiplegia, aphasia, hemianesthesia, and homonymous hemianopsia. Six weeks following the injection of the serum he was hospitalized for investigation and custodial care. He had regained some power in the right leg, but was still unable to move the right upper limb, and was aphasic, with the field defect persisting. In the second patient the cerebral damage was of similar nature, but was much milder in degree, with a reasonably good functional recovery and little residual change. These cases are comparable in every way to nine previously reported in the literature. The authors speculate on the nature of the lesions in these patients and say that the reported cases of allergic encephalitis, myelitis, and neuritis with serum sickness show considerable similarity to the nervous system reactions of acute virus exanthema, infectious mononucleosis, and collagen diseases.

Sensitivity to Tubocurarine and Decamethonium in Myasthenia Gravis.—The purpose of the experiments described here was to determine and compare equipotent doses of tubocurarine and decamethonium in normal subjects and in patients with myasthenia gravis. It was hoped that by interpretation of the effects of these agents in the light of the difference in their mode of action at the neuromuscular junction, some insight might be gained into the abnormal physiology in myasthenia gravis. Threshold paralytic doses of tubocurarine and decamethonium were determined in 30 patients with myasthenia gravis and in 22 nonmyasthenic subjects. Patients with myasthenia gravis (mean threshold dose 5.42 μg per kilogram of body weight) were 5.5 times as sensitive to tubocurarine as were nonmyasthenic subjects (mean threshold dose 24.77 μg per kilogram). About 3 to 4% of normal subjects are as sensitive to tubocurarine as an average patient with myasthenia gravis, and about 3 to 4% of patients with myasthenia gravis are not abnormally sensitive to threshold doses of tubocurarine. Patients with myasthenia gravis were not more sensitive to decamethonium than were nonmyasthenic subjects. With subthreshold doses of decamethonium, patients experienced transient amelioration of signs and symptoms. Results obtained are consistent with the concept that the fundamental feature of myasthenia gravis is a blockade of the neuromuscular junction by a substance or process that decreases the muscular response to acetylcholine.

Effect of Edrophonium in Myasthenia Gravis.—Edrophonium (Tensilon) chloride is one of the quaternary ammonium salts that exert a stimulatory effect on the neuromuscular junction. It is capable of antagonizing the neuromuscular blockade produced by *d*-tubocurarine. The organic phosphates, such as tetraethylpyrophosphate, act only by their anticholinesterase effect; neostigmine has both a direct stimulating effect at the myoneural junction and an anticholinesterase effect; and edrophonium acts primarily by direct stimulation at the myoneural junction and only secondarily as an anticholinesterase agent. Thirteen patients with myasthenia gravis and four controls were given intravenous injections of 10 or 15 mg. of edrophonium; three received additional doses orally, while one patient also received intramuscular injection of the drug. Increase in strength began within 30 seconds after intravenous administration, or as soon as it could be tested, and increased to a maximum within 1 to 10 minutes. The effect began to decline after 10 minutes, but there was a secondary rise of lesser degree. The effect of the injection lasted less than one hour in most patients. Grip strength increased from 90 to a maximum of 200 lb. in the patients with myasthenia gravis. Clinical improvement correlated favorably with this and was sometimes spectacular. Side-effects were mild. No patient with myasthenia gravis had fasciculations, though the control group did experience them. There was improvement in strength regardless of the previous medication, but the increase seemed to be greater in those who previously took tetraethylpyrophosphate than in those who were receiving neostigmine. The control subjects also experienced a prompt increase in strength, even though it was of small magnitude. The secondary rise noted in most tests may represent the minor anticholinesterase action of the drug. After intramuscular injection of edrophonium, the response became apparent within 10 minutes, attained the maximum in about an hour, and then declined over a period of three to five hours. Strength was fairly well maintained by injections of 50 mg. every three to four hours. Reactions to the intramuscular medication were minimal. A measurable increase in strength resulted also from the oral administration of 50 to 250 mg. doses. The effect began within 30 to 60 minutes and lasted several hours. The patient discontinued the oral medication because of headaches. The authors conclude that edrophonium seems to offer a new approach to the study of myasthenia gravis, based on pharmacological action unrelated to anticholinesterase activity.

Northwest Medicine, Seattle

52:173-264 (March) 1953

This Age of Tension: Environment and Human Action. R. T. Johnstone.—p. 195.
*Program for Selection of Patients for Mitral Commissurotomy. R. A. Bruce, D. L. Rodgers and K. A. Merindino.—p. 201.
Anaphylactic Shock in Penicillin Therapy. K. Chapman and D. Metheny.—p. 207.
Cholesterol and Cystic Duct Obstruction in Pathogenesis of Gall Stones. J. M. Roberts.—p. 208.

Selection of Patients for Mitral Commissurotomy.—According to Bruce and co-workers, commissurotomy should not be done simply because a patient has a characteristic murmur of mitral stenosis on auscultation. The following four point program has been employed by the authors for selection of patients for mitral commissurotomy. 1. Accurate clinical diagnosis of mitral stenosis must be made. Usually percussion or chest x-ray examination demonstrates that the left border of the heart is straightened due to enlargement of the pulmonary

conus, artery, and left auricle. The first heart sound at the apex and the second sound at the base to the left of the sternum are accentuated. There are variable murmurs, such as mid- and late-diastolic murmurs at the apex, an occasional systolic murmur at the left sternal border (arising from the pulmonary artery), as well as an early diastolic murmur of pulmonary insufficiency (Graham Steell murmur). Murmurs may vary with posture, arrhythmias, respiration, and fibrotic and calcific changes in the mitral valve. Demonstration of the moving calcified valve shadow during fluoroscopy is confirmatory. 2. Clinical evidence of need for surgery depends on symptoms of pulmonary engorgement and diminished working capacity. Cardinal symptoms are dyspnea, orthopnea, cough, and hemoptysis. Fatigue is the earliest evidence of decreased working capacity; inability to perform the customary daily activities is a more advanced sign, and clinically apparent heart failure is a far-advanced sign. In the absence of these indications for commissurotomy, surgical intervention for mitral stenosis is justified in a woman of the childbearing age with a history of congestive heart failure during pregnancy, or in a patient with a history of repeated arterial emboli who is likely to have a recurrence that might cause a serious, or even fatal complication, and in whom auricular appendectomy is proposed prophylactically. 3. Clinical contraindications to mitral commissurotomy are recent and uncontrolled acute rheumatic fever, subacute bacterial endocarditis, intractable heart failure, or the presence of pronounced aortic stenosis, mitral insufficiency, left ventricular enlargement, or left axis deviation of the electrocardiogram. 4. The decision to intervene surgically also depends on the optimal time for commissurotomy. When there is virtually no risk from operation, there is usually no need for it; on the contrary, when the need is greatest, the risk is also maximal. Then appropriate laboratory tests may provide quantitative data that will aid the physician in making this important decision. Much can be learned from clinical evaluation of symptoms and signs, chest fluoroscopy, pulmonary function studies, and phonocardiography. Although cardiac catheterization provides considerable information regarding intracardiac and pulmonary hemodynamics, more practical information that aids the clinical management of these patients has been obtained from serial exercise tolerance tests. By the latter technique, it has been possible to evaluate quantitatively not only the need and the optimal time for surgery but also the degree of improvement following operation.

Pediatrics, Springfield, Ill.

11:191-308 (March) 1953. **Partial Index**

*Effect of Magnesium Sulfate on Renal Dynamics in Acute Glomerulonephritis in Children. J. S. Harris and W. J. A. DeMaria.—p. 191.
Idiopathic Celiac Disease: I. Mode of Onset and Diagnosis. D. H. Andersen and P. A. di Sant' Agnese.—p. 207.
Id.: II. Course and Prognosis. P. A. di Sant' Agnese.—p. 224.
*Incidence of Gross Visual Defects Due to Retrolental Fibroplasia. E. R. Schlesinger and I. McCaffrey.—p. 238.
Dominant Inheritance of Diabetes Insipidus: Family Study. C. B. Pender and F. C. Fraser.—p. 246.
*Clinical Diagnosis of Endocardial Fibrosis: Analysis of Literature with Report of Four New Cases. E. C. Lambert, C. N. Shumway and K. Terplan.—p. 255.

Magnesium Sulfate in Acute Glomerulonephritis.—Magnesium sulfate has been used extensively in the therapy of acute glomerulonephritis in children. The few studies of the mode of action of the drug demonstrated that the magnesium ion is responsible for the beneficial effects on the hypertension and encephalopathy. The studies described here aimed to determine the effect of magnesium sulfate on the renal dynamics of normal children and of those in the hypertensive and convalescent phases of acute nephritis. Inulin and sodium para-aminohippurate clearances were used as indicators of the glomerular filtration rate and of effective renal plasma flow. Magnesium caused no changes in the renal function of normal children, but in children with acute nephritis, the glomerular filtration rate and effective renal plasma flow were markedly subnormal during the hypertensive stage and increased toward normal during convalescence. The intravenous administration of magnesium sulfate caused marked rises in the glomerular filtration rate and in effective renal plasma flow when given during the hypertensive stage. Magnesium produced smaller rises in effective renal plasma flow but no changes in the glomerular filtration rate when given during convalescence. The implications of these findings are discussed. It is suggested that renal vasospasm is present in children with acute glomerulonephritis and that adequate therapy with magnesium sulfate relaxes this vasospasm.

Gross Visual Defects Due to Retrolental Fibroplasia.—The incidence of gross visual defects due to retrolental fibroplasia was studied among infants born during 1948 and 1949 to residents of New York State, exclusive of New York City. Since it was not feasible to study all of the nearly 300,000 infants, only those whose birth weights were less than 2,000 gm. and who survived to the age of 4 months were selected for study. Questionnaires were sent to the mothers of the selected infants. Information was obtained on 3,377 infants, or 92.1%, of the 3,667 selected for study. A total of 50 cases of gross visual defects due to retrolental fibroplasia was found. The incidence rates decreased from 15.9% in the birth weight group under 1,000 gm. to 4.3% in the 1,000 to 1,499 gm. group, and 0.7% in the 1,500 to 1,999 gm. group. The infants reported as having the shortest periods of gestation were found to have the highest incidence, the rate in the group with a period of gestation under seven months being 7.6% as compared with a rate of 0.3% in the group whose gestation period was reported as eight months or more. The incidence of gross visual defects was not related to the occurrence of complications during the mother's pregnancy. The incidence was slightly higher in males than in females, and also slightly higher in the infants of mothers over 30 years of age.

Clinical Diagnosis of Endocardial Fibrosis.—Endocardial fibrosis (also termed endocardial sclerosis and endocardial fibroelastosis) is now recognized as a pathological entity occurring in infants and having a grave, if not universally fatal, prognosis. Previous publications have dealt chiefly with the morphological aspects, the possible cause, and the mechanism of cardiac failure. It has been differentiated as a pathological entity from the group of diseases termed idiopathic cardiac hypertrophy. The purpose of this communication is to discuss the diagnostic possibilities and to describe four cases seen by the authors in the past two years. Evidence is presented that indicates that endocardial fibrosis is a relatively common cause of death from heart disease in infancy and that a presumptive diagnosis of this condition can often be made during life. The salient features are age under one year, marked dyspnea without persistent cyanosis, absence of a loud cardiac murmur on repeated examinations, enlargement of the heart, presence of femoral pulsations, and electrocardiographic evidence of left ventricular hypertrophy in the precordial leads. The chief conditions to be considered in the differential diagnosis are aberrant coronary artery, interstitial myocarditis, and glycogen storage disease of the heart, all of which are much less frequent as proved by necropsy studies. In two of the four cases described here, the diagnosis was made before death.

Proc. Staff Meet. Mayo Clinic, Rochester, Minn.

28:145-192 (March 25) 1953

SYMPOSIUM ON INTRACEREBRAL ELECTROGRAPHY

Technic of Depth Electrography. H. W. Dodge Jr., C. B. Holman, C. W. Sem-Jacobsen and others.—p. 147.
Depth Distribution of Normal Electro-Encephalographic Rhythms. C. W. Sem-Jacobsen, R. G. Bickford, M. C. Petersen and H. W. Dodge Jr.—p. 156.
Some Effects of Barbiturate Anesthesia on the Depth Electrogram. R. G. Bickford, A. Faulconer Jr., C. W. Sem-Jacobsen and others.—p. 162.
Human Olfactory Responses Recorded by Depth Electrography. C. W. Sem-Jacobsen, R. G. Bickford, H. W. Dodge Jr. and M. C. Petersen.—p. 166.
Depth Electrogram in Schizophrenic Patients. M. C. Petersen, R. G. Bickford, C. W. Sem-Jacobsen and H. W. Dodge Jr.—p. 170.
Studies on Electrical Structure and Activation of Epileptogenic Focus. R. G. Bickford, H. W. Dodge Jr., C. W. Sem-Jacobsen and M. C. Petersen.—p. 175.
Observations on Depth Stimulation of Human Brain Through Implanted Electrographic Leads. R. G. Bickford, M. C. Petersen, H. W. Dodge Jr. and C. W. Sem-Jacobsen.—p. 181.
Neurosurgical and Neurologic Application of Depth Electrography. H. W. Dodge Jr., A. A. Bailey, R. G. Bickford and others.—p. 188.

Southern Medical Journal, Birmingham, Ala.

46:207-314 (March) 1953

Shwartzman Phenomenon When Modified by Nitrogen Mustard, Adrenocorticotrophic Hormone (ACTH), and Thorium Dioxide: Histopathologic Study. G. J. Race and D. W. Reed.—p. 207.
*Curling of the Esophagus. M. Eskridge and J. D. Peake.—p. 213.
Selective Tendon Transfers for Recurrent Clubfoot. E. B. Carpenter and S. H. Huff.—p. 220.
Comments on Present Day Management of Syphilis. R. H. Kampmeier. —p. 226.
Degenerative Diseases with Nutritional Interrelationships. T. D. Spies. —p. 238.
Diabetes and Tuberculosis. A. Reaud.—p. 248.
Role of Chemotherapy in Management of Malignant Lymphomas and Leukemias. R. W. Rundles, W. B. Barton and E. V. Coonrad.—p. 259.
Newer Antibiotics in Treatment of Rectal Strictures of Lymphogranuloma Venereum. L. Banov Jr.—p. 269.
Experiment in Industrial Foot Health. M. R. Gasque and G. F. Holt. —p. 275.
Medical Emergencies in General Practice. J. R. Bender.—p. 279.
*Carbon Dioxide Therapy. G. A. Silver.—p. 283.
Benign Pigmented Nevi: Survey of Treatment by Dermatologists. C. Shaw.—p. 286.
Certain Aspects of Cesarean Problem. D. G. Tollefson.—p. 290.
Femoral Embolectomy. F. T. Wallace, W. F. Utterman and W. T. Hendrix.—p. 296.
Basis for Therapy of Common Skin Diseases. G. Bednar.—p. 298.

Curling of the Esophagus.—The condition referred to here as curling of the esophagus has been referred to also as pseudodiverticulum, segmental spasm, spastic pseudodiverticula, functional diverticula, spasmodic stricture, and diffuse spasm of the lower half of the esophagus. Roentgenograms made at the right moment show that the esophagus has a corkscrew or coiled appearance. When the patient swallows barium under the fluoroscope and the bolus reaches the lower half of the esophagus, there suddenly appear numbers of ring-shaped constrictions that may completely occlude the lumen, moving neither up nor down. This usually precedes the first peristaltic wave, and when it arrives, the portion above the tight constriction distends until some of the barium is regurgitated above the peristaltic wave. In some patients the pressure is so great that diverticulums are seen to protrude and become permanent. The etiology of curling is obscure and many theories have been postulated, some of which are cited. The patient's chief complaint is usually dysphagia. Pain is referred to an area behind the lower half of the sternum. It may also go posteriorly into the mid-dorsal region. It sometimes extends upwards to the anterior thorax, neck, either external auditory meatus, or jaw. It may be centered in the epigastrium. It is usually associated with eating or drinking. Roentgenologically the condition is usually easily recognized but associated disease of the esophagus, particularly carcinoma, must be ruled out. This may sometimes prove impossible because the esophagoscope cannot be passed beyond the constricting rings. Treatment is not very satisfactory. Esophagoscopy is said to give partial relief. Repeated dilatation has helped to some extent. Psychotherapy with relief of nervous tension has helped. Atropine is usually not effective. Citing therapeutic observations of several other observers, the authors say that morphine sulfate given intravenously caused relief for several hours, amyl nitrate transitory relief and amphetamine (Benzedrine) sulfate relief for about an hour followed by worsening. A combination of hyoscyamine 0.45 mg., atropine sulfate 0.04 mg., and scopolamine hydrobromide 0.01 mg., one tablet twice a day, gave relief to patients who had associated parkinsonism. Amphetamine sulfate 5 mg. every 4 hours for 36 hours gave complete relief to two patients. The 19 cases presented here were observed among a group of 2,295 patients in whom fluoroscopy of the esophagus was done. The average age of these patients was 66 years, the youngest was 49, and the oldest 84 years. The authors feel that in an aging population this condition will be found quite frequently.

Carbon Dioxide Therapy.—This report is concerned with the effect of carbon dioxide therapy in 250 patients (treated since February, 1951), most of whom had psychoneurotic disturbances. There were no psychotic patients in this group, which included many with mild depression in a form usually viewed as neurotic or reactive; some with anxiety in which depression, if present, seemed secondary to the anxiety; some with hysterical reactions without outspoken disturbances in affect; an obsessive-compulsive-phobic group often showing anxiety; and finally a miscellaneous group of patients with alcoholism, stuttering, or organic lesions and a neurotic overlay. The treatment consisted of inhalations of a 30% carbon dioxide and 70% oxygen mixture and was given by the method advocated by Meduna in 1943. After October, 1951, the treatment was modified for some patients. It was necessary to induce coma for the treatment to be effective. The number of inhalations (25 to 40) necessary to induce coma in some depressed and some anxious patients tended to accentuate the anxiety. Nitrous oxide (N_2O) was used as a preliminary anesthesia. This was much easier to breathe. After eight or nine inhalations, transfer was effected to the carbon dioxide and oxygen mixture and coma was rapidly induced. The 15 to 25 inhalations of the carbon dioxide and oxygen mixture, after the preliminary nitrous oxide, usually produced some decrease of the depression or amelioration of anxiety symptoms. The treatment was effective in about 45% of the patients and an additional 25% reported slight but definite improvement. The effect of the treatment is sustained, since the 100 cases followed for 6 to 12 months show the same proportion of improvement as the 100 cases followed for from 12 to 20 months.

46:315-404 (April) 1953

Double Contrast Studies of Colon: Polyps in Children. C. W. Yates. —p. 315.
Value and Uses of Gastroscopy. T. J. Manson.—p. 319.
Vertical Flap Ureteropelvioplasty: Preliminary Report. P. L. Scardino and C. L. Prince.—p. 325.
*Ten Years Experience in Surgical Management of Cancer of Lungs. A. R. Diaz and H. Anido.—p. 332.
Primary Meningeal Melanomas. S. Russi, C. Robinson and B. Nagler. —p. 336.
*Venous Catheterization of Heart in Selection of Patients for Mitral Commissurotomy. D. W. Chapman, R. H. Skaggs, I. M. Johnson and others.—p. 343.
Steroid Hormones and Collagen Diseases. T. B. Schwartz, F. L. Engel and W. M. Nicholson.—p. 347.
Adrenal Insufficiency in Newborn Male Infants. B. P. Briggs, E. H. Crawley and V. L. Toombs.—p. 351.
Pheochromocytoma. W. H. Gerwig Jr. and S. F. Seeley.—p. 355.
*Results of Three Years Experience with New Concept of Baby Feeding. W. W. Sackett Jr—p 358
Development of Vision and Its Relation to Muscle Anomalies. G. S. Ellis and R. L. Waugh Jr.—p. 363.
Differential Diagnosis of Deafness. L. W. Alexander.—p. 372.
Management of Third Stage of Labor. J. E. Savage.—p. 379.
Long Acting Intercostal Nerve Block: Safer Method of Anesthesia for Abdominal Surgery. R. W. Bartlett and D. W. Eastwood.—p. 385.
Acute Pancreatitis: Diagnosis and Treatment. H. L. Bockus, A. Bogoch and J. L. A. Roth.—p. 388.

Cancer of Lungs.—Of 94 male and 6 female patients between the ages of 11 and 68 with cancer of the lung observed in Cuba during the last 10 years, 94 were treated by thoracotomy and only 6 were rejected for surgery because of metastasis to supraclavicular lymph nodes or other organs. In 22 of these 94 patients a resection was not possible; 69 underwent total pneumonectomy and 3 lobectomy. Microscopic examination of the tumor was done in 77 cases and revealed squamous cell carcinoma in 49, adenocarcinoma in 25, oat cell carcinoma in 2, and 1 alveolar cell carcinoma. Of the 69 patients who had pneumonectomies, only 18 were free from involvement of the mediastinal lymph nodes; this latter group had the best survival rates. There were four operative deaths, and four patients died while still in the hospital. Of the remaining 64 patients, 1 survived for eight years, 1 for six years, 15 for four years, 19 for three years, 14 for two years, 10 for one year, and 4 for six months. These survival rates compare favorably with results obtained with surgical treatment of cancer of other organs. The authors' 71% resectability rate is much higher than that in three other series of patients with cancer of the lung previously reported by leading surgeons in the United States. The authors believe that this difference can be explained by the fact that their first patient was operated on in 1942 at a time when the general practitioner had been alerted by countless papers on the early diagnosis and surgical treatment of cancer of the lung and thoracic surgery was well developed. Early diagnosis and early exploratory thoracotomy determine the success of surgical treatment of cancer of the lung.

Selection of Patients for Mitral Commissurotomy.—Of 36 rheumatic patients with predominantly mitral stenosis who were studied by venous catheterization of the right side of the heart and by cardiac output determination, 30 were treated by commissurotomy. Two of the 30 died. Indications for commissurotomy as suggested by cardiac catheterization were ascertained as follows: (1) elevated "pulmonary capillary pressure" at rest, increasing with exercise; (2) elevated pulmonary arterial pressure at rest and during exercise; (3) reduced cardiac output at rest, with little or only slight increase during exercise; (4) arteriovenous oxygen difference elevated above normal, both in the resting and exercise states; (5) increased pulmonary arteriolar resistance and total pulmonary resistance; (6) mitral valve area decreased below 1.5 sq. cm. as calculated by the formula of Gorlin and Gorlin.

New Concept of Infant Feeding.—A new infant feeding regimen that rapidly converts a six hour feeding schedule to a three-meal-a-day regimen, and introduces food other than milk as early as the second day of life has been employed in 300 infants in Miami, Fla., during the past three years. Results showed that the new regimen was gratifying to its users and also a source of medical interest as these infants continued to follow closely and sometimes even surpassed the physical standards set up by babies on a more conservative routine. A more detailed survey, now in progress, would seem to emphasize the results of the author's preliminary survey done over one year ago. In addition these results would seem to be equally satisfactory in infants fed by this schedule but not under the author's direct supervision.

Southwestern Medicine, El Paso, Texas

34:73-108 (March) 1953

Poliomyelitis. W. E. Coggeshall.—p. 87.
Our Job in 1953. T. C. Terrell.—p. 92.

34:109-148 (April) 1953

Treatment of Intra-Oral Carcinoma. J. M. Ovens.—p. 129.
Case of Obstruction of Duodenum Resembling Superior Mesenteric Artery Syndrome. D. D. Gain and A. R. Uzel.—p. 133.

Texas State Journal of Medicine, Fort Worth

49:123-204 (March) 1953

Accidental Death: Challenge to Modern Pediatrician. G. B. Forbes.—p. 127.
Twenty-Seven Years of Cataract Surgery in Review. W. E. Vandevere.—p. 131.
Glaucoma in Aphakia. A. A. Nisbet.—p. 134.
*Tobacco-Alcohol (Toxic) Amblyopia. H. W. Maxwell.—p. 137.
Status of Positive Contact Orbital Implants. R. C. House.—p. 141.
Surgery of Nose in Relation to External and Internal Nasal Deformities. J. C. Dickson and B. T. Withers.—p. 145.
Establishment of Criteria for Selection of Alcoholic Patients for Antabuse Therapy. G. C. Randall and W. C. Rogers.—p. 151.

Tobacco-Alcohol Amblyopia.—Tobacco-alcohol (toxic) amblyopia is characterized by bilateral impairment of central vision with a centrocecal scotoma initially for red and green and with an intact peripheral field. Tobacco and alcohol usually act in conjunction, though amblyopia may develop from the use of either. Most cases of tobacco-alcohol amblyopia seem to come on after a depression in general health such as physical depression, undernutrition, or, less commonly, an acute illness. The histories of two patients with tobacco-alcohol amblyopia are presented. The general health of these two men, aged 32 and 57, respectively, was impaired, probably as the result of improper diet. Partial loss of central vision, bilateral scotomas, and inability to distinguish red and green traffic lights were the most important eye symptoms. By diminishing their tobacco and alcohol consumption slightly and with a proper diet, including vitamin B_1, one patient recovered completely and the other partially. Apparently the vitamin B deficiency was the most important factor, and the author is unable to say to what extent tobacco and alcohol were causative factors. If the use of alcohol and tobacco is continued, visual failure may increase, and some permanent optic atrophy may develop. Sometimes a tolerance is acquired and vision may remain the same or improve slightly. No patient becomes blind. With abstention from tobacco and alcohol, and with a proper diet, vision improves.

Virginia Medical Monthly, Richmond

80:189-250 (April) 1953

Medullary Nailing in Fractures. W. M. Deyerle.—p. 191.
Trends in Surgical Treatment of Pulmonary Tuberculosis: Study of 106 Cases of Pulmonary Resection. E. C. Drash and L. B. Brown.—p. 198.
Diverticulosis of Jejunum: Frequently Overlooked Source of Gastrointestinal Bleeding. H. J. Warthen.—p. 203.
Use of Rehabilitation Medicine in Complete Treatment of Hemiplegia. A. R. Dawson.—p. 206.
Treatment of Burns. C. H. Lupton.—p. 209.
*Acute Barbiturate Intoxication—with Case Report. W. H. Higgins Jr.—p. 218.
Vioform—Its Use in Dermatologic Therapy. W. H. Kaufman.—p. 222.
Rapidly Fatal Hodgkin's Disease. W. H. Harris Jr.—p. 225.
Clinical Management of Pulmonary Invalid. W. H. Barney.—p. 228.
Paracentesis Abdominis. M. B. Hiden.—p. 231.

Acute Barbiturate Intoxication.—That the use of barbiturates and their derivatives is increasing is evidenced by the fact that the production of these drugs was 68% higher in 1951 than in 1940. Poisoning by barbiturates is likewise increasing. After briefly commenting on the pharmacology of barbiturates, Higgins discusses the etiology, symptomatology, and treatment of barbiturate poisoning. Treatment of barbiturate intoxication consists of gastric lavage, adequate oxygenation, prophylactic use of antibiotics, prevention of atelectasis and aspiration by keeping a patent bronchotracheal airway and frequent turning, and maintenance of proper fluid balance. Specific therapy includes the use of the amphetamines and picrotoxin. Picrotoxin, in the author's opinion, is the drug of choice. This powerful central nervous system stimulant can be safely given if administration is discontinued promptly at the first signs of muscular or nervous stimulation. It is short acting, being excreted in about 20 minutes. For this reason and because in the presence of barbiturate intoxications larger doses are easily tolerated, large doses should be given almost hourly until the patient remains responsive between injections. The author directs special attention to the synergism between alcohol and barbiturates, the case presented emphasizing the dangers of their concomitant use. Treatment consisted chiefly of administration of picrotoxin, and the woman recovered; however, severe narcosis and even death may occur when only one-half the lethal dose of each drug, alcohol and a barbiturate, is combined. Many poisonings result from ignorance of this fact.

Western J. Surg., Obst. & Gynecology, Portland, Ore.

61:93-148 (March) 1953

Diagnosis of Tumors of Pituitary Body. J. Raaf and W. M. Craig.—p. 93.
Routine Smears—Practical Method for Cytodetection of Unsuspected Cervical Cancer. P. L. Martin, T. A. Slate and J. W. Merritt.—p. 102.
Etiology and Treatment of Abdominal Distension. R. E. McKechnie.—p. 106.
Prolapse of Gastric Mucosa Through the Pylorus: Its Surgical Corrections. J. E. Strode.—p. 111.
Some Endocrine Effects of Neostigmine. C. F. Fluhmann.—p. 116.
Routine Use of Pubocervical Fascia in Uterine Suspensions. H. E. Dedman.—p. 129.

West Virginia Medical Journal, Charleston

49:95-116 (April) 1953

Orthopedic Treatment of Arthritis. L. T. Peterson.—p. 95.
Use of Procaine Amide Hydrochloride in Treatment of Penicillin Reaction. A. J. Gianascol.—p. 98.
Reevaluation of Previously Treated Syphilis Cases. S. S. Lee.—p. 99.
Spontaneous Changes in Presentation of Fetus During Last Half of Pregnancy. R. T. Rapp.—p. 101.

Wisconsin Medical Journal, Madison

52:165-218 (March) 1953

Some New Points in Cochlear Anatomy and Their Physiologic Implications. A. C. Hilding.—p. 165.
Homicide as Manifestation of Thalamic or Hypothalamic Disorder with Abnormal Electroencephalographic Findings. E. D. Schwade and O. Otto.—p. 171.
Protein Needs in Children, Premature and Pre-School Groups. E. T. McEnery.—p. 175.
Antihistaminic Drugs in Dermatology. J. J. Barrock.—p. 179.
Transverse Presentation. J. E. Sinsky.—p. 184.

FOREIGN

Annals of Rheumatic Diseases, London

12:1-80 (March) 1953

Rheumatism: National Problem. Lord Horder.—p. 1.
Rheumatic Complaints in an Urban Population. J. H. Kellgren, J. S. Lawrence and J. Aitken-Swan.—p. 5.
Intravenous Colchicine in Management of Gouty Arthritis. W. Graham and J. B. Roberts.—p. 16.
Clinical Studies of Phenylbutazone (Butazolidin) and Butapyrin (Irgapyrin) in Rheumatoid Arthritis, Rheumatoid Spondylitis, and Gout. E. G. Kidd, K. C. Boyce and R. H. Freyberg.—p. 20.
Radiotherapy in Arthritis. M. H. L. Desmarais.—p. 25.
Gold, Sodium, and Liver Function in Rheumatoid Arthritis. G. D. Kersley, L. Mandel and M. R. Jeffrey.—p. 29.
*Rheumatoid Arthritis Treated with "Irgapyrin": Analysis of 20 Cases. G. Achari, B. Mukopadhaya and P. Sengupta.—p. 32.
*Proseptasine in Treatment of Rheumatoid Arthritis. L. J. Barford.—p. 35.
Effect of an Anti-Histamine in Rheumatoid Arthritis. D. C. Wilson.—p. 38.
Marie-Strümpell Spondylitis in Women. T. L. Tyson, W. A. L. Thompson and C. Ragan.—p. 40.
Effects of ACTH on Peripheral Blood Flow in Rheumatoid Arthritis. J. W. Beattie and A. Woodmansey.—p. 43.

Rheumatoid Arthritis Treated with Irgapyrin.—It is known that under nonspecific stress the pituitary gland liberates corticotropin, which in turn stimulates the adrenal cortex to secrete cortical hormones with specific actions. Of these the glucocorticoids that ameliorate the symptoms of rheumatoid arthritis are the most important. It is presumed that nonspecific agents that are effective in rheumatoid arthritis bring about the amelioration of symptoms by stimulating the pituitary-adrenocortical system. On this hypothesis, Irgapyrin (a mixture of equal parts of phenylbutazone and aminopyrine) was given a therapeutic trial in 4 men and 16 women between the ages of 16 and 38 with rheumatoid arthritis. Nine of the 20 patients in whom the duration of the disease varied from four to six months had a 69.83% reduction in their total circulating eosinophils four hours after the injection of the drug, and in these patients the drug brought about almost complete relief from pain and muscular stiffness. Five patients with arthritis of from 8 to 10 months' duration had a 57.89% fall in circulating eosinophils. Improvement was less pronounced in the latter group; pain and tenderness did not completely subside and some residual stiffness of the affected joints remained. Two patients with arthritis of more than 12 months' duration had a 46% reduction in the circulating eosinophils and no significant amelioration of symptoms. In the remaining four patients whose disease had been present for two and a half years, Irgapyrin did not produce any significant reduction of circulating eosinophils or any improvement in symptoms. The amelioration of symptoms by Irgapyrin thus was directly proportional to the duration of the disease. The patients who improved showed a statistically significant reduction in the circulating eosinophils four hours after the Irgapyrin injection. This suggests that the drug acts by stimulating the pituitary-adrenal system. Patients who did not improve had no fall in circulating eosinophils.

Proseptasine in Treatment of Rheumatoid Arthritis.—Benzylsulphanilamide ("proseptasine") in doses from 0.5 gm. three times daily to 0.25 gm. twice daily with nine dried yeast tablets or 1 tsp. (about 4 cc.) of proteolysed liver daily as vitamin B supplement was given to 49 women and 10 men with rheumatoid arthritis. Follow-up was complete in 44 of 59 cases; 27 of these patients were aged 50 or more, and 17 were aged less than 50. The duration of the disease ranged from 3 months to 25 years, and the duration of treatment with "proseptasine" from 1 to 46 months. Of these 44 patients, 32 were improved, 11 were unchanged, and 1 became worse. Of 12 patients treated for a year or longer, 11 were improved and one was unchanged. The relapse rate, when the drug was discontinued, was high, and relapses occurred within a few weeks. When treatment was resumed, the response to the drug was the same as before. There was no constant effect on the blood sedimentation rate. Toxic side-effects occurred in five patients, so that administration of the drug had to be discontinued. Prolonged treatment did not adversely influence the blood picture. Although the series was too small for drawing definite conclusions, it would appear that "proseptasine" may help to hold rheumatoid arthritis in check until a remission occurs.

Archiv f. Hygiene u. Bakteriologie, Munich

137:1-78 (No. 1) 1953. **Partial Index**

Contribution to Bacteriology of Anaerobic Corynebacteria and Their Occurrence in Pathological Material. H. Seeliger.—p. 1.
Second Contribution to Problem of Mechanism of Infection with Neurotropic Types of Virus. M. Nikolitsch.—p. 11.
Small Shigella Dysenteriae Epidemic in Münster District. P. vor dem Esche.—p. 20.
*Course of and Observations in Rural Epidemic of Poliomyelitis. A. Klaila.—p. 43.

Rural Epidemic of Poliomyelitis.—The occurrence of an epidemic of poliomyelitis in three adjacent rural districts of Upper Franconia, Germany, during the period from May to October, 1952, is reported. Of 83 male and 60 female hospitalized patients, 79 (55%) were between the ages of 1 and 7 years, 37 (26%) between the ages of 8 and 18 years, and 27 (19%) between the ages of 19 and 40 years. Nine of the 11 deaths (a mortality rate of 7.7%) occurred in small children and only 2 in adults. Meningism was the predominant symptom in most of the patients. Prolonged phenomena of irritation occurred occasionally in addition to pareses. In general the disease was severer during the first weeks of the epidemic than during the last weeks; pareses occurred more frequently in the beginning of the epidemic, while later on the aparetic-encephalitic type was observed more frequently. The clinical course showed a tendency favorable to regression. The author considers it as highly significant that there was a high incidence of infection in persons who shared the same home, as well as in members of a whole group owing to direct contact with patients or to contact with asymptomatic carriers. Contact could be proved in 52 of the 143 hospitalized patients, and 13 chains of contact or groups of patients could be demonstrated. Thus contagiousness has been demonstrated, and careful observation of the routes of infection convinced the author that the temporary and constant carriers of the virus play a predominant part in causing by various means of transmission sporadic cases of poliomyelitis. On the other hand, the patients with the acute disease may be responsible for the occurrence of the disease in whole groups, first through direct contact (infection by droplets during the presence of respiratory manifestations) and later on by dust infection or flies. In contrast to previous observations the epidemic reached its peak in July, while there was only a mild secondary flare-up in August and September. The period of the highest incidence was characterized by abnormal dryness and heat, a very low water level in rivers and streams, and a severe fly plague. As a result of his experience the author emphasizes that officially controlled measures of quarantine are imperative as a preventive means in combatting the epidemic. Research should be directed to the early control of carriers of the virus.

Belgisch Tijdschrift voor Geneeskunde, Leuven

9:193-236 (March) 1953

Pulmonary Cancer: III. Attack on Lung Cancer. R. Korteweg.—p. 193.
Catheterization of Heart: Its Use in Study of Acquired Heart Disease K. Vuylsteek, R. Pannier, A. Van Loo and J. Verstraeten.—p. 198.
*Presacral Induction of Pneumoperitoneum. J. Bekaert, G. Mortier and C. Van Beylen.—p. 212.

Presacral Induction of Retropneumoperitoneum.—Bekaert and associates review the history and evaluate various techniques for roentgenologic visualization of the parenchymatous organs in the retroperitoneal space, pointing out that the presacral method of insufflation was developed and first described in 1947 and 1948 by R. Rivas of Spain. They show that this method of extraperitoneal pneumography is excellent for the visualization of the adrenals, kidneys, spleen, liver, and psoas shadow. It is valuable also in the study of the pancreas and of the abdominal portion of the esophagus. It provides an easy way of inducing pneumomediastinum, and some authors assert that its preoperative use simplifies interventions on the rectum, sigmoid, kidney, and spleen because it separates the various layers. With all these advantages, the presacral insufflation technique of R. Rivas involves no greater danger than any other method of examination.

British Journal of Dermatology, London

65:77-120 (March) 1953

Case of Allergic Cutaneous Vasculitis (Arteriolitis Allergica). M. Ruiter. —p. 77.
*Observations on Persistence of Skin Sensitivity with Reference to Nickel Eczema. J. K. Morgan.—p. 84.
Structures Resembling Fuseaux in Case of Ringworm of Scalp Due to Microsporum Canis Bodin and Microsporum Audouini Gruby. G. Daniels.—p. 95.

Skin Sensitivity in Nickel Eczema.—Among 58 patients with contact dermatitis who reacted positively to patch tests with one drop of 10% nickel sulfate solution there were only two in whom the primary source of the sensitivity was industrial (nickel plating). Nickel-plated garters were the source in 55 patients, and a nickel-plated watch in one patient. The eruption in many of these patients involved not only the primary site of sensitization but also other sites where nickel was in contact with the skin as a result of the wearing of earrings, brooches, necklace clasps, medallions, metal watch straps, and even safety pins. Furthermore 31 of these patients when first seen had secondary eczematous spread to sites other than those in contact with nickel, particularly to the elbow flexures, face, and neck. The sensitivity of 54 of these patients was reassessed after an interval ranging from 1½ to 11 years. Persisting sensitivity was confirmed in 31 by the presence of contact eczema with continued exposure, or freedom if contact was avoided; 23 patients gave negative results to patch testing for nickel sensitivity, but 18 of these continued to have eczema. It is suggested that in some of these patients, the specific sensitivity to nickel was merely a transitory phase in a series of eczematous reactions, many of them nonspecific in character. The prognosis of patients with positive patch tests to nickel involved many factors; in some it appeared to be independent of the continuance of contact with nickel. Apparently the constitutional background is often of greater prognostic significance than the specific external agent.

British Medical Journal, London

1:633-686 (March 21) 1953

Changing Concepts of Health and Disease, with Particular Reference to "Psychosomatic Medicine." R. R. Bomford.—p. 633.
Anti-Curare Agents. A. R. Hunter.—p. 640
Use of Intravenous Ergometrine to Prevent Post-Partum Haemorrhage. J. D. Martin and J. G. Dumoulin.—p. 643.
Haemoglobin Levels in Group of Elderly Persons Living at Home Alone or with Spouse. W. Hobson and E. K. Blackburn.—p. 647.
Clinical Trial of Phenylindanedione as Anticoagulant. M. Toohey.—p. 650.
Treatment of Nausea and Vomiting of Pregnancy with Antihistamines. S. Lask.—p. 652.
Acute Nitrobenzene Poisoning with Transient Amino-Aciduria. W. E. Parkes and D. W. Neill.—p. 653.
Acute Tetrachlorethane Poisoning: Report on Two Fatal Cases. A. K. Mant.—p. 655.
Anal Fistula with Extension to Thigh. E. Wilson.—p. 656.
Polyposis of Small Intestine with Pigmentation of Oral Mucosa: Report of Two Cases. A. P. Kitchin.—p. 658.

Canadian Medical Association Journal, Montreal

68:319-422 (April) 1953

Report of a Cancer Study, 1949. R. P. Vivian.—p. 319.
Anatomist as a Witness. I. M. Thompson.—p. 327
Tuberculosis in Recent Immigrants O. T. Cheung.—p. 330.
Complications of Blood Transfusion. B. P. L. Moore.—p. 332.
Clinical Study of a New Sulfonamide in Treatment of Urinary Infections. J. P. Bourque and J. Joyal.—p. 337.
Treatment of Hypertension with Oral Hexamethonium. C. B. Rich and W. H. Holubitsky.—p. 342.
Haematological Values in Elderly People. D. M. Jefferson, W. W. Hawkins and M. C. Blanchaer.—p. 347.
Carcinoma Stomach—The Case for Total Gastrectomy. A. A. Klass. —p. 350.
Heart Disease and Pulmonary Tuberculosis. G. Phillips.—p. 353.
Cardiac Compression from Funnel-Chest (Chone-Chondrosternon). A. Vogelsang.—p. 356.
Use and Misuse of Plaster Walking Boot. O. Rostrup.—p. 360.
*Retroversion of Uterus as a Normal Position. I. A. Perlin.—p. 363.
Electrocardiographic Response to Standard 2-Step Exercise Test. J. Wener, A. A. Sandberg, L. Scherlis and others.—p. 368.

Retroversion of Uterus.—Of 92 women with retroversion of the uterus treated by suspension at the Victoria General Hospital in Halifax between 1925 and 1946, only 44 were followed up. Of these 44, 20 had uncomplicated retroversion, and of these, only 7 (35%) obtained complete relief from their symptoms following the operation. Twenty-four patients had associated with the retroversion some other complicating factor such as cervical erosion, cervicitis, cervical laceration, or fibroid, for which surgical intervention was also done. The uterus in all these patients was mobile. In this group 14 patients (60%) obtained complete relief of their symptoms. The authors feel that the cures obtained in these patients were due to the other surgical intervention rather than to the suspension. In a survey of 2,157 women delivered in the department of obstetrics of Dalhousie university in the last 26 years no evidence was found that the uterus observed to be retroverted at the 8th or 10th day of the puerperium drains less efficiently than the anteverted uterus. In 16 patients found to have a retroverted uterus at the seventh day post partum, in 8 (50%) it had become anteverted by the sixth week. The author believes that in a considerable number of women a change in position from ante- to retroversion and vice versa occurs continually. More medium and small than large uteri were found to be retroverted at the 10th day and at the 6th week post partum. It would seem, therefore, that neither is retroversion caused by a large uterus nor does retroversion itself cause the uterus to be large. There was no evidence that puerperal women with retroversion are more likely to have complaints referrable to delivery at the sixth week post partum than the women with an anteverted uterus. There was no clear-cut evidence that retroversion predisposes to or is usually associated with uterine prolapse. It has been the author's policy never to treat a retroversion at the 10th day or 6th week post partum by pessary replacement or knee-chest position. Of 1,118 women delivered between 1928 and 1949 whose uteri were never replaced or supported with a pessary when found retroverted, 24 attributed to their delivery certain complaints such as backache and low abdominal pain. Of these 24 women, 13 were examined at the 10th day post partum and the uterus was found retroverted in only one; seven were examined at the sixth week and the uterus was found retroverted in three. Three of the 1,118 women have had suspensions done. One, whose uterus was not retroverted, had the suspension for prolapse; the two others had the operation done for sterility and neither became pregnant. It is suspected that all these findings may be equally true of the retroverted uterus in the nulliparous women, since the incidence of retroversion seems to be the same in nulliparous as in parous women. As a result of his experience, the author believes that retroversion is a normal position for the women in whom it occurs, and that, unless complicated by such conditions as endometriosis or tender prolapsed ovaries that cause dyspareunia, it is no more likely to produce symptoms than the anteverted organ. Surgical treatment of an uncomplicated retroverted uterus is unlikely to relieve the symptoms attributed to the retroversion.

Deutsche Zeitschrift für Nervenheilkunde, Heidelberg

169:421-506 (No. 6) 1953. **Partial Index**

Total Circulation and Cerebral Blood Perfusion in Intracranial Angiomas and Aneurysms. A. Bernsmeier and K. Siemons.—p. 421.
Medicinal Treatment of Myasthenia. H. Bauer and O. Schmid.—p. 427.
*Results of Liver Function Tests in Organic Nervous Diseases. C. Faust. —p. 438.
Disturbances of Metabolism and Central Nervous System. G. Peters. —p. 446.

Liver Function Tests in Organic Nervous Diseases.—A series of liver function tests were employed in 119 patients with diseases of the nervous system in an attempt to study the entire functional spectrum of the liver. Included in the series were the thymol turbidity test, cholesterol test, zinc sulfate test, Takata-Ara test, galactose tolerance test, hippuric acid test, and paraoxyphenylpyroracemic acid tolerance test. Determinations of serum bilirubin and urobilinogen were made, and the excretion of azorubin was tested. In patients with postencephalitic parkinsonism the results of the tests suggested latent impairment of the liver, while only minor deviations from the normal were observed in patients of advanced age with parkinsonism. In patients with paralysis agitans liver function was not disturbed. In nearly all the patients with multiple sclerosis disturbance of the liver function was indicated by the results of the paraoxyphenylpyroracemic acid tolerance test, the hip-

puric acid test, and the galactose tolerance test (liver-specific tests); the thymol turbidity test and the cholesterol test revealed considerable deviations from the normal. The results of these two latter tests paralleled the course of the disease. In patients with hereditary degenerative diseases deviations from normal could not be detected with the liver-specific tests, and the results of the lability tests did not lend themselves to evaluation. In patients with polyneuritis, the results of the tests varied with the pathogenesis. Patients with polyneuritis associated with chronic alcoholism had positive results from the galactose tolerance test, while patients with severe Landry's paralysis and with great increase in the protein in the cerebrospinal fluid without corresponding increase in cells (as in Guillain-Barré syndrome) had negative results from the specific liver function tests. Nearly three-quarters of the patients with nonspecific inflammatory diseases of the nervous system had positive results from the paraoxyphenylpyroracemic acid tolerance test, thymol turbidity, and cholesterol test. To do justice to the variety of the metabolic process, it seems important to use many methods of examination in order to determine the significance of disturbed partial function of the liver in diseases of the nervous system.

Journal of Tropical Medicine and Hygiene, London

56:49-72 (March) 1953

Some Observations on Intestinal Parasites of Man and Their Diagnosis. L. Freedman.—p. 49.
Antibiotic Treatment of Infective Gangrene of the Mouth. D. B. Jelliffe. —p. 53.
*Fluorosis in the Butana, Sudan. D. A. Smith, H. A. Harris and R. Kirk. —p. 57.
An Antidote to Scorpion Toxin. A. H. Mohammed and M. el Karemi. —p. 58.

Fluorosis in the Sudan.—A focus of endemic fluorosis was discovered in the Sudan during an investigation into health and nutrition at Abu Deleig in the Butana desert in December, 1952. During the examination of schoolboys, aged 7 to 14 years, many instances of abnormality of the dental enamel were noted. These were characteristic of fluorosis and were provisionally diagnosed as such. Grade 1 changes included white, opaque, chalky areas of the enamel of permanent teeth that were most commonly seen on the cusps of premolars and first molars and on the distal half of the central and lateral incisors. Grade 2 changes included dark yellow-brown discoloration, often in a pattern of broad horizontal bands or wavy parallel lines, that were most prominent in the upper incisors. Grade 3 changes were pitting and mottled discoloration of the enamel, mainly on the incisors. Grade 1 changes were found in 39.6% of 134 boys, grade 2 in 17.1%, and grade 3 in 3.7%, the total incidence being 60.4%. The incidence of caries was low. The incidence of dental fluorosis in adults was similar to that in the children. Nine out of 10 samples of well water contained fluorine in concentrations between 1.10 and 4.00 parts per million.

Lancet, London

1:555-606 (March 21) 1953

Problem of Peptic Ulceration. H. Ogilvie.—p. 555.
Involvement of Autonomic Nerve-Fibres in Diabetic Neuropathy. M. M. Martin.—p. 560.
Specificity of Incomplete "Cold" Antibody in Human Serum. H. Crawford, M. Cutbush and P. L. Mollison.—p. 566.
Isolation of Pituitary Antidiuretic Peptide and Similar Urinary Peptide by Paper Chromatography. G. C. Arneil and H. E. C. Wilson.—p. 568.
Treatment of Delirium, Psychosis, and Coma Due to Drugs. J. Gould. —p. 570.
Investigation of Antituberculous Substances: Agar Diffusion Method Using Mycobacterium Smegmatis. M. B. King, R. Knox and R. C. Woodroffe.—p. 573.
Effect of Butazolidine on Excretion of Water and Electrolytes. J. Green and P. O. Williams.—p. 575.
*Syndrome Associated with Ingestion of Chemically "Improved" Flour. G. C. Sheldon and A. Yorke.—p. 577.

Allergic Response to Chemically "Improved" Flour.—The authors present a detailed history of a woman, aged 50, who had no personal or family history of allergic disorders but who had had a skin disorder since 1940. The chronic eruption involved the face and neck and also the upper limbs symmetrically; it was subject to acute irregular exacerbation, and pruritus was troublesome during the acute phase. Because of the appearance of the hands, she was treated for dysidrotic eczema but did not respond. Because depression was a dominant feature of the recurring skin episodes, accompanied by sporadic flushing, neurodermatitis associated with the climacteric was thought of, but despite varied treatment the condition persisted until 1952, with occasional exacerbations. In March, 1952, she noticed that when she came into contact with flour, it increased the severity of her existing lesions, but the result of a flour-free diet indicated that ingestion rather than external irritation was responsible. An authority on the chemistry of milling provided bread prepared from flour not treated with chemicals, and the eating of such bread caused no skin lesions. Whenever she ate bread made from flour treated with nitrogen trichloride, the lesions on hands, arms, face and neck became manifest within 24 hours. The skin irritation was generally accompanied by mental disturbances in the form of insomnia, irritability, and what the patient herself identified as "a morose depression." An alternative to nitrogen trichloride for the chemical treatment of flour is chlorine dioxide, and so the authors decided to ascertain the effect on their patient of flour treated with this chemical. The woman was given bread prepared from flour treated with chlorine dioxide unknown to her. Within three hours of eating this bread, she had pruritus of the hands and forearms, and within 24 hours there was pruritus of face and neck, which felt "dry and tight," together with anorexia and insidious mental depression. Examined after 48 hours, she presented essentially the same clinical picture as that following ingestion of flour treated with nitrogen trichloride, but some of the symptoms, particularly the constitutional ones, such as anorexia, were severer. The question arises of whether this is a rare case of allergy or merely the first recognition of a common disorder.

Maandschrift voor Kindergeneeskunde, Leyden

21:41-72 (Feb.) 1953

*Administration of Corticotropin (ACTH) and Cortisone in Rheumatic Carditis. S. van Creveld and F. Kuipers.—p. 41.
Erythroblastosis Fetalis and Blood Group Kell. J. J. van Loghem Jr., H. de Raad and A. van Hattem.—p. 63.

Corticotropin and Cortisone in Rheumatic Carditis.—Van Creveld and Kuipers show that the prognosis of rheumatic carditis becomes more unfavorable as the number of relapses increases. Fatalities from this disease are due chiefly to the sequelae, that is, to valvular lesions. Apart from the prevention of relapses by prophylactic methods, the authors feel that improvement in prognosis will be effected mostly by early treatment of the rheumatic carditis with corticotropin and cortisone. From a survey of the literature the authors gained the impression that early treatment with adequate doses can prevent persistent damage, such as valvular lesions, in a considerable number of cases. They present the histories of seven patients in whom they employed cortisone. Two children died, but in two others a fatal outcome was prevented by the treatment. All children showed evidence of a valvular lesion after treatment was completed, despite the fact that it was instituted within two weeks after the first clinical signs of cardiac involvement appeared. From the literature, the authors gained the impression that corticotropin might be more effective than cortisone in preventing valvular lesions.

Minerva Medica, Turin

44:365-404 (Feb. 14) 1953. **Partial Index**

Pathology of Difficult Child and Only Child. F. Copello.—p. 365.
*Behavior and Measurement of New Antituberculous Preparation Derived from Combination of Streptomycin with Congo Red: Study of Spinal Fluid of Persons with Tuberculous Meningitis. G. Pescetti and E. Destefanis.—p. 369.
First Clinical Results of New Drug in Treatment of Coronary Insufficiency. P. Cantù and F. Tibaldi Chiesa.—p. 372.
*Hepatorenal Fatty Degeneration Caused by Aureomycin. A. Pagliei. —p. 384.

Streptomycin Combined with Congo Red in Tuberculous Meningitis.—Streptomycin combined with congo red in a 1:9 ratio was given to two persons with tuberculous meningitis to study the meningeal permeation and evaluate the levels and

the elimination curves of the antibiotic in the spinal fluid. In one of the patients the blood levels were also determined. After one intravenous injection of 0.5 gm., the streptomycin level in the spinal fluid was 2 μg per cubic centimeter and it doubled within the second hour. In the blood, however, the concentration was lower, and it did not increase after the first hour. Moreover, the antibiotic was not present in the blood 10 hours after the injection, whereas it was still found in small traces in the spinal fluid 24 hours later. The preparation seems to become fixed electively in the inflamed meninges, and since the transudate current proceeds from the blood to the fluid, the higher levels that were found in the latter are easily understood. When after 24 hours an additional 0.5 gm. was injected, the streptomycin level in the spinal fluid was 8 to 10 μg per cubic centimeter, but 24 hours later it was again 4 to 5 μg. This dose was repeated every 24 hours for several days, and a cumulative effect was observed; however, 24 hours after the injection never more than 4 to 5 μg of streptomycin were found per cubic centimeter of fluid. The cumulative effect in the fluid is analogous to the effect it had in the tissues as the authors had previously demonstrated in another study. After the first two days of therapy, the fluid, like the tissues, assumed a pinkish color, which became progressively red. The intensity of the color was directly proportional to the concentration of the preparation in the fluid.

Fatty Degeneration of Liver After Aureomycin Therapy.—A 7-year-old girl was hospitalized in severe general condition with acute diffuse peritonitis due to a perforating appendicitis. Successful laparotomy was performed, and the early postoperative course, during which the patient was given aureomycin in addition to other medications, was good. On the day of the operation and the first and second postoperative days she received intravenously 100 mg. of the drug every four hours (an average of 24 mg. per kilogram of body weight), and on the third and fourth days 250 mg. orally every four hours (an average of 60 mg. per kilogram of body weight). A total dose of 4,800 mg. was given. The patient's general condition was improving and recovery seemed to be assured, when suddenly on the sixth postoperative day, elevated temperature, tachycardia, dyspnea, mild diffuse edema, subicterus at the sclera, and signs of hemorrhagic diathesis were observed. Small amounts of black urine containing large quantities of albumin and urobilin, and hyaline and granular casts were passed. The Takata-Ara test indicated pronounced liver damage. A picture of hepatorenal coma developed, and the patient died on the eighth postoperative day. At autopsy all signs of peritoneal inflammation had disappeared. The liver, however, was greatly enlarged, tender, flabby, doughy, and opaque dark yellowish colored. Microscopic examination revealed fatty degeneration that was more pronounced near the Kiernan's spaces; the trabeculae could no longer be distinguished, but there were no alterations in the capsule. The kidneys were also slightly enlarged but had a normal consistency; dark yellowish lines could be seen through the capsule. The child had recovered completely from peritonitis, but had died of acute hepatorenal insufficiency secondary to fatty degeneration of the liver caused by the toxic effects of aureomycin. The author suggests that the degenerative effect of aureomycin on some essential organs is due not to a toxicity intrinsic to the drug itself but rather to the peculiar constitution and the specific reaction of some allergic persons. Excessive doses and the intravenous route of administration may also be responsible for these side-effects.

Wiener medizinische Wochenschrift, Vienna

103:181-198 (March 7) 1953. **Partial Index**

*Prolonged Controlled Hypotension, Contribution to Conservative Treatment of Intracranial Hemorrhages and Acute Cerebral Hypertension. L. Schönbauer, R. Kucher and K. Steinbereithner.—p. 185.
Controlled Hypotension with "Depressin" (Hexamethonium Preparation) and "Pendiomid." A. Benke.—p. 187.
Dysmenorrhea From Social Medical Point of View. K. Bockhorn.—p. 189.

Prolonged Controlled Hypotension in Treatment of Intracranial Hemorrhages.—Depressin, a proprietary hexamethonium chloride preparation, was employed to produce prolonged controlled hypotension in a 39-year-old woman in her third attack of apoplexy and in a 43-year-old woman who after an attack of influenza suddenly had become unconscious and paralyzed on her left side. In the first patient the blood pressure was maintained for 12 hours at 80/55; this induced hypotension was produced by intravenous injection of a total dose of 380 mg. of the ganglion-blocking agent and postural ischemia combined with continuous administration of oxygen. After seven hours of controlled hypotension Babinski's sign and clonus disappeared on the left side. After nine hours Babinski's sign disappeared also on the right side, but recurred after 11 hours, and the patient died suddenly 12 hours after the start of the controlled hypotension. Necropsy revealed hypertrophy of both ventricles, general vascular sclerosis, a recent focus of softening in the right internal capsule, and old foci of softening in the basal ganglions. In this case, the disappearance of the pathological reflexes during controlled hypotension is to be considered noteworthy. In the second patient who was in deep coma with symptoms of acute cerebral hypertension and increasing deterioration of her general condition, the systolic blood pressure of 240 mm. Hg was reduced to 50 mm. Hg by the intravenous administration of an initial dose of 60 mg. of hexamethonium chloride, and blood pressure was maintained for 17 hours at values varying from 40 to 60 mm. Hg by the administration of a total dose of 300 mg. of the drug. The systolic blood pressure then gradually rose to 80 mm. Hg and remained at this level until 25 hours had passed from the start of the induced hypotension. The patient then awakened and orientation was perfect. After 10 hours of controlled hypotension, paresis and Babinski's sign had disappeared. Arteriography of the carotid artery and lumbar encephalography did not reveal definite pathological changes. Lumbar puncture revealed more than 500 leukocytes and a high protein content in the spinal fluid. A tentative diagnosis of encephalitis was made, the patient was treated with antibiotics, and she was discharged free of complaints six weeks after admission to the hospital. The patient died six weeks later, and necropsy revealed diffuse demyelination of the white matter of the hemispheres, severe lesions of the basal ganglions, and neuronal degeneration of the brain stem.

Zentralbl. Arbeitsmed. u. Arbeitsschutz, Darmstadt

3:1-32 (Jan.) 1953. **Partial Index**

Question of Liver Damage After Trinitrotoluol Poisoning. H. Meyeringh and A. Dietze.—p. 4.
*Examination of Lead Line in Ultraviolet Light. F. Dangl, O. Frank and V. Lachnit.—p. 6.
Poisoning with Lead Tetraethyl: Case Reports. K. Müller.—p. 8.
Caution with Aluminum Dust: Unexpected Explosion. K. Flick.—p. 9.
Chronic Intoxications in the Manufacture of Moth Remedies Consisting Chiefly of Paradichlorobenzene. K. Wallgren.—p. 14.
Prophylaxis of Poisoning by Fluorides During Welding. O. Hettche and H. Merck.—p. 15.

Examination of Lead Line in Ultraviolet Light.—The lead line at the gums of patients with lead poisoning represents a deposit of lead sulfide that results from the action of hydrogen sulfide, which is present in the mouth (particularly if teeth are not kept clean), on the lead albuminate excreted by the capillaries of these patients. This results in a bluish black discoloration at the edge of the gum. Stimulated by reports on fluorescence phenomena in the oral cavity, particularly the red fluorescence of dental tartar, Dangl and associates examined the gums of persons with and without lead poisoning under ultraviolet illumination. In a definite lead line there appeared under the ultraviolet light a dark zone that differed from the bluish fluorescing gums. In one patient with lead poisoning the dark line was seen to gradually disappear while he received treatment for lead poisoning. In some doubtful cases a narrow lead line could be clearly differentiated from dental tartar under the ultraviolet light, but in others in whom examination under ordinary light suggested a lead line, examination under ultraviolet light clearly demonstrated merely the red fluorescence of dental tartar. The authors admit that the bismuth line, which may develop in patients receiving bismuth in the treatment of syphilis, cannot be differentiated from the lead line under ultraviolet light, but the occupational and clinical history should explain whether lead, bismuth, or mercury is the cause.

BOOK REVIEWS

Hypnosis in Modern Medicine. Edited by Jerome M. Schneck, M.D., Clinical Associate in Psychiatry, College of Medicine, State University of New York, Brooklyn. Cloth. $7.50. Pp. 323. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto, 2B, 1953.

Since the first child was rhythmically crooned to and rocked by its mother and since the first patient was calmed and soothed by the first medicine man, suggestion and hypnosis have retained their essential place among the healing arts. The variegated heritage of such therapeutic practices has never quite lost its magical attraction. Proof of this are the four main derivatives of Mesmer's "animal magnetism" today: the cults of the "magnetic belt" and devices still sold by the millions to the gullible; Christian Science as derived from Mesmer through his disciples Phineas Quimby and Mary Baker Eddy; psychoanalysis via the hypnotists Charcot and Bernheim and their student Sigmund Freud; and the current vogue of hypnosis itself. The wishful yearnings underlying such regressively esoteric approaches to therapy have given rise, since Mesmer's death, to thousands of books on hypnosis; this volume is the latest.

According to its editor, the distinguishing characteristic of this book is that each section was written by an expert with special experience in his subject. The first chapter, a historical account of medical hypnosis written by George Rosen, sets a high standard by reviewing the unscientific origins and fantastic nature of much of the theory about hypnotic phenomena. Unfortunately, many of the other contributors seem not to have studied this introduction very carefully; indeed, William T. Heron, in his section on instruction in hypnosis, states "Actually, there is little in the history of the subject which is useful to the modern practitioner" (page 289). In line with this, the various intervening chapters on hypnosis in internal medicine, surgery, anesthesiology, obstetrics and gynecology, and dentistry repeat a pattern that is now familiar to the serious student of hypnology; a pattern of clinical daring leading to striking observations of significant phenomena, unfortunately followed too often by uncontrolled interpretations and overenthusiastic therapeutic inferences. As exceptions to this, the chapters by Schneck and by Ambrose on hypnosis in adult and child psychiatry are good surveys by writers obviously familiar with special techniques, but, here again, the work of others is too often accepted on purely impressionistic bases. With regard to the physiological substrate of hypnosis, M. J. Bass, after a somewhat diffuse review of the literature, concluded, "Although hypnosis differs from sleep at the present time, however, reliable criteria for distinguishing hypnosis from the waking condition are not available" (page 251).

The volume is well documented and indexed and should be a useful addition to the reference library of any psychiatrist, psychologist, or research worker already active in the field. Some of its contents, however, may be misleading to general practitioners, medical students, and others who, without specialized training and experience, may attempt to apply certain of its recommendations to clinical practice.

Hearing Aids: Their Use, Care, and Repair. By Matthew Mandl. Cloth. $3.50. Pp. 158, with 64 illustrations. The Macmillan Company, 60 Fifth Ave., New York 11, 1953.

The construction and operation of the modern electronic hearing aid are presented briefly and simply in this short book. It is well illustrated with photographs and line drawings and should be of interest to hearing aid users who have some knowledge of radio electronics. The physician, audiologist, and hearing aid salesman interested in basic hearing aid principles will find this book a helpful introduction to the subject.

The reviews here published have been prepared by competent authorities and do not represent the opinions of any official bodies unless specifically stated.

Textbook of Virology for Students and Practitioners of Medicine. By A. J. Rhodes, M.D., F.R.C.P., Research Associate, Connaught Medical Research Laboratories, School of Hygiene, University of Toronto, Ontario, and C. E. van Rooyen, M.D., D.Sc., M.R.C.P., Research Member Connaught Medical Research Laboratories. Second edition. Cloth. $8. Pp. 561, with 76 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

This textbook covers viral as well as rickettsial infections of both man and animals, with emphasis on human diseases caused by or associated with these agents. The authors have wisely avoided the unsettled formal classification of viruses and rickettsias by grouping the subject matter according to the regional and clinicopathological characteristics of the infections. The first and larger portion of the book is devoted to virus infections and is introduced by a discussion of their fundamental characteristics, response to specific therapy, and laboratory diagnosis. The general biological character of rickettsias is similarly presented to introduce the smaller portion of the text. Discussions of both types of infection are presented under the names of the diseases, a feature that will appeal to medical students and practitioners. The authors present the following aspects of each disease: clinical features, pathology and pathogenesis, epidemiology, properties of the causal agent, immunity, specific treatment, and laboratory diagnosis. Ample space is given to discussion of the immunologic reactions important in the diagnosis and study of viruses and rickettsias. The authors are obliged to utilize numerical and alphabetic symbols that have been introduced to identify various strains and types of these micro-organisms, but the retention of such clinical abbreviations as LGI for lymphogranuloma inguinale (venereum), EKC for epidemic keratoconjunctivitis, CCA for chick cell agglutination, and HA for hemagglutination tests should not be encouraged. The abbreviation ACTH is also employed in place of the adopted generic name, corticotropin.

The second edition of this textbook will be welcomed by teachers, students, and physicians as a highly practical source of basic information for both introductory and advanced studies of the subject. Each section is followed by references, and the general index is arranged for convenience in locating the available information. At the time of printing, the results of the recently reported studies on the prophylactic use of gamma globulin in poliomyelitis were not available to the authors.

Commotio Cerebri: Cerebral Concussion and the Postconcussion Syndrome in Their Medical and Legal Aspects. By Cyril B. Courville, M.D., Director, Ramon Cajal Laboratory of Neuropathology, Los Angeles County Hospital, Los Angeles. Cloth. $5.25. Pp. 161, with 12 illustrations. San Lucas Press, 316 N. Bailey St., Los Angeles 33, 1953.

This is a practical book for students and practitioners. It is of special value to attorneys and expert witnesses, those who have to deal with the problem in court. The author has reviewed not only the medical but also the general literature. He has drawn many descriptive references to the symptomatology of concussion from legends, folk tales, and history. It is clear that concussion has been universally recognized as a distinct clinical entity. The review shows how physicians related themselves to the problem and how knowledge of the subject slowly developed through the centuries.

The author is impressed by the fact that persons who suffer from simple concussion too often are not adequately compensated, and that attorneys and physicians employed by insurance companies frequently decide that affected patients are intentionally attempting to defraud.

The book is particularly valuable in its analysis of the mechanism of concussion. Symptoms, diagnosis, and management are adequately discussed. Two distinct schools of thought have arisen; one concludes that all post-traumatic symptoms are to be explained on an organic basis; the other, at the opposite extreme, assumes that all post-traumatic symptoms in concussion are purely functional and should be ignored.

The author concludes that the characteristic residual symptoms of commotio cerebri cannot be lightly dismissed as malingering or a compensation neurosis; that, while purely psychic postconcussional manifestations may also occur, the counterfeit need not be confused with the genuine; and that an intelligent, comprehensive therapeutic approach to the problem has potentialities for quicker relief of the patient's symptoms and for lowering of cost to insurance carriers.

Practical Clinical Chemistry: A Guide for Technicians. By Alma Hiller, Ph.D., Associate Attending Biochemist in Charge of Clinical Chemistry, Presbyterian Hospital of City of Chicago. Cloth. $6.50. Pp. 266. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto, 2B, 1953.

This book is well written, and the style is simple enough so that even the technician untutored in chemistry may easily use it. An outline for each procedure follows a comprehensive narration and explanation of the principles and techniques involved. These outlines are reprinted on detachable, perforated sheets at the back of the book for the convenience of the technician.

The selection of methods is generally excellent. The only controversial method is that for the estimation of nonprotein nitrogen of blood. The hypobromite deamination method presented is certainly simpler than the old micro-Kjeldahl method, but there is much contradictory literature concerning it, and at least one researcher reports yields as low as 78% of the true nonprotein nitrogen content with the hypobromite deamination method. The author has selected many methods that require the use of a spectrophotometer. For some time, spectrophotometers have been within the economic reach of analytical laboratories; however, for those laboratories still not equipped with spectrophotometers, the usefulness of this book might have been extended by presenting, for each colorimetric assay, an alternate procedure in which a visual colorimeter is used. It should be made quite clear, however, that the superior accuracy of the spectrophotometer is adequate reason for its selection over a colorimeter if the choice can be made.

Dysarthic Speech (Speech in Cerebral-Palsy). By Emil Froeschels, M.D., President, International Society for Logopedics and Phoniatrics, New York. Cloth. $3.75. Pp. 172, with 34 illustrations. Expression Co., Publishers, Magnolia, Mass., 1952.

Defective speech, particularly in the cerebral palsy patient, is considered in this text. The anatomic lesions of the central nervous system and the vocal mechanisms that account for dysarthric speech are presented briefly. The use of proper neuroanatomic nomenclature in the rather limited discussions requires that the lay speech therapist, for whom the book is primarily written, have a good basic understanding of neuroanatomy in order to gain much from this portion of the text. The congenital dysarthrias and those acquired early in childhood are considered from the symptomatic and therapeutic standpoint. These same basic principles may also be applied to the dysarthrias resulting from injuries and cerebrovascular accidents in adults. The format of the book is attractive, and it is illustrated with simple line drawings. Much interesting reference material is also included.

Preventive Aspects of Chronic Disease: Conference Proceedings, March 12-14, 1951, Chicago, Illinois. Sponsored by Commission on Chronic Illness. Co-Sponsors: National Health Council, U. S. Public Health Service. Paper. $2.50. Pp. 311. Health Publications Institute, Inc., Raleigh, N. C., 1952.

This is a report of the conference of physicians, social workers, and others representing 43 organizations interested in prevention of chronic disease. These diseases are characterized by permanence, residual disability from some acute condition, and an irreversible disease process. Special instruction is necessary for the patient and all who attend him in order that some degree of rehabilitation might be obtained. A long period of observation, supervision, and care must be expected. This involves early diagnosis, thorough and complete cure of the acute condition if possible, and follow-up from the social as well as the medical side of the problem. The physician is not always sure when he has cured a patient completely. Symptoms may subside, but the condition may become permanent before anyone is fully aware of what has happened. Multiple sclerosis and poliomyelitis are examples of such conditions, and chronic arthritis is always possible in any case of acute rheumatism.

Prevention is the keynote of this 300 page monograph, but all of its authors are well aware of the limitations of the word. Seventeen diseases are discussed, and the factors of heredity, predisposition, and carelessness and neglect through ignorance and willful disregard of the principles of hygiene and sanitation are considered. Much of the present knowledge of chronic diseases is included, along with problems that require further study, analysis, and integration.

Plastic Surgery at the New York Hospital One Hundred Years Ago with Biographical Notes on Gurdon Buck. By Herbert Conway, M.D., and Richard B. Stark, M.D. Forewords by John Hay Whitney, Stanhope Bayne-Jones, M.D., and Frank Glenn, M.D. Cloth. $5. Pp. 110, with 30 illustrations. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33rd St., New York 16, 1953.

This small volume tells the story of the development of plastic surgery at the New York Hospital 100 years ago. It is the story of Gurdon Buck, bold and imaginative surgeon, who is regarded as the pioneer of plastic surgery in the United States. Buck is probably remembered by the medical profession mainly for "Buck's extension" and "Buck's fascia," but his most important contributions were in the field of plastic surgery. In 1876 he wrote an important treatise on the subject that was translated into three languages. This book is attractively printed and is illustrated with photographs of patients operated on by Buck. It should be of interest to surgeons and to the medical profession in general.

The Biochemistry of Gastric Acid Secretion. By Edward J. Conway, M.D., D.Sc., F.R.S., Professor of Biochemistry and Pharmacology, University College, Dublin, Ireland. Publication number 119, American Lecture Series, monograph in Bannerstone division of American Lectures in Biochemistry and Biophysics. Edited by W. Bladergroen, Jr., M.A., Ph.D. Cloth. $6.50. Pp. 185, with 29 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, 1953.

Dr. Conway deals with the site of gastric secretion, with ways of stimulating it, with various theories that have been advanced on its formation, both from a chemical standpoint and from the standpoint of energetics, and with the protective role of gastric urease. Except for five pages on the treatment of gastric ulcer with urea, the book does not include therapy. Throughout the book, parietal cells and yeast cells are compared; obviously the latter are easier to study, and more is known of their biochemical processes. The writing is clear, and the illustrations are adequate. The material is made available through a detailed table of contents, summaries for each chapter, and indexes. The bibliography is 10 pages long. Printing and binding are excellent.

Doctor in the House. By Richard Gordon (pseud.). Cloth. $2.75. Pp. 186. Harcourt, Brace and Company, Inc., 383 Madison Ave., New York 17, 1953.

In this amusing, nostalgic account of the life, labors, and loves of an English medical student in one of London's hospitals, the author describes with gentle humor his struggles with his studies, his trials with some of his teachers, escapades with fellow students, flirtations with nurses, clinical trial and error with the help of patients, and drinking bouts at the King George pub. Some parts of the book are highly entertaining. There is, for example, the colorful description of the nurse in charge of obstetrics students who could talk only about mothers and newborn infants and thought of everyone solely as a reproductive mechanism. When discussing obstetric anatomy she always awarded the parts of the birth canal to the listener. "When your cervix is fully dilated," she cautioned the medical students, "you must decide whether to apply your forceps to your baby. You must feel to see if your head or your breech is presenting." And in response to the question "Suppose it's your shoulder or your left ear?" she replied without hesitation, "Then you put your hand in your uterus and rotate your child." There is much more in a similar vein. This book can provide several hours of enjoyable reading.

QUERIES AND MINOR NOTES

EXCRETA FROM TOILETS ON TRAINS

TO THE EDITOR:—*About two years ago, I read that the nation's railway trains, as a result of their open plumbing, may be disseminating poliomyelitis virus throughout the country. At a pediatric meeting in Danville, Pa., I talked with other physicians who have wondered about this. It should be possible, by adding a dye to the water in train toilets, to determine the amount of contamination. Has any such study been made?* *M.D., New York.*

This inquiry was referred to two consultants, whose respective replies follow.—ED.

ANSWER.—A quantitative study of human excreta flushed from toilets on railway passenger cars was made a few years ago under the auspices of the Joint Committee on Railway Sanitation of the Association of American Railroads' operation and maintenance department. A brief summary of the findings and references to the original reports may be found in an editorial on "Railroad Toilet Wastes" (*J. A. M. A.* **137:**1134 [July 24] 1948). There appears to be no substantial direct evidence of the importance of railroad toilet wastes in the spread of poliomyelitis.

ANSWER.—The most recent authoritative large scale survey of this problem was conducted by the sanitary research project of the Joint Committee on Railway Sanitation, on which were representatives of the United States' and Canada's public health services and the engineering, mechanical, and medical sections of the Association of American Railroads. The results of that study, which involved over four years of research and experimentation, were as follows: 1. No evidence was found that sewage wastes from railroad passengers have caused outbreaks or epidemics of communicable enteric disease. 2. The presence of coliform bacteria in railroad ballast, in runoff from roadbeds, and in the atmosphere of fast-moving trains is no greater than in other environments generally considered not inimical to good health. 3. The amount of fecal solids discharged to the railroad right of way from passenger trains is exceedingly small; it is estimated to average for all passengers in the United States less than 1 oz. per yard (91.4 cm.) of track per year. It was pointed out, however, that whether any undetected relationship actually exists between present disposal methods and the enteric diseases and possibly poliomyelitis-like diseases is not known at present. The report proposed that the problem be studied continuously and that hoppers be provided for transitory retention of waste in certain areas in which the deposition may conceivably constitute a hazard, despite the inability to demonstrate one objectively. None of the authorities consulted by the project personnel believed that railroad passenger waste plays a significant part in the spread of poliomyelitis. In about 10,000 references reviewed by members of the project, the role of the railroads in this connection was mentioned six times, but in none was more suggested than that railroad toilet waste may possibly be a reservoir of the virus.

REFERENCES

Railroad Wastes and Poliomyelitis, unpublished report by the Sanitation Research Project, Association of American Railroads, Baltimore, 1949.

Sewage Wastes From Railroad Passenger Cars, Summary Report to the Joint Committee on Railway Sanitation, Sanitation Research Project, Association of American Railroads, Baltimore, May 31, 1950.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any official bodies unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

TREATMENT OF NEUROSYPHILIS

TO THE EDITOR:—*What is the modern viewpoint on the treatment of cerebral and meningovascular syphilis? Is penicillin alone sufficient in every case? What tests indicate a cure, in view of the fact that some patients have irreversible abnormal Lange gold curves, positive blood Wassermann test reactions, and, perhaps, positive spinal fluid Wassermann test reactions? One patient shows hypersensitivity (reaction not indicated on her chart) to penicillin. Does this indicate use of the older form of treatment with arsenic, or is oxytetracycline (Terramycin) therapy worth trying?*

Thomas M. Shannon, M.D., Morganton, N. C.

ANSWER.—It is difficult to answer these questions without some preliminary clarification. By "meningovascular and cerebral syphilis" it is assumed the inquirer means neurosyphilis. There are a number of accepted classifications of neurosyphilis, all of which are considerably more detailed than the two terms employed in the question. Most syphilologists and neuropsychiatrists would agree on some such simple classification as the following one: (1) asymptomatic neurosyphilis, early (infection less than four years in duration); (2) asymptomatic neurosyphilis, late (infection more than four years in duration; (3) acute syphilitic meningitis (usually a manifestation of early syphilis); (4) diffuse meningovascular neurosyphilis; (5) tabes dorsalis; (6) dementia paralytica (general paralysis of the insane); (7) other rarer manifestations, such as Erb's spinal spastic paraplegia and vascular neurosyphilis. "Asymptomatic neurosyphilis" means, of course, neurosyphilis manifested only by abnormalities in the spinal fluid, without neuropsychiatric symptoms or signs.

Penicillin may be used in the treatment of all types of central nervous system syphilis and may be administered by various systems. One is to administer aqueous penicillin G to the hospitalized patient, in a dose of from 100,000 to 500,000 units or more every three to four hours, around the clock, to a total dose over 10 to 14 days of 10 million units or more. Many competent observers now treat most patients with neurosyphilis on an ambulatory basis, utilizing a repository penicillin preparation, usually procaine penicillin G in aqueous suspension or an oil with 2% aluminum monostearate added. Also usable for this purpose are the penethamate hydriodide (Neo-penil) and N,N'dibenzylethylenediamine dipenicillin G (Bicillin). The particular advantage of penethamate hydriodide has been reported to be appearance of a greatly increased concentration of penicillin in the cerebrospinal fluid following intramuscular administration and the advantage of Bicillin to be unusual prolongation of therapeutic blood levels (7 to 10 days) after a single intramuscular injection of 600,000 units. With any of the repository penicillin preparations, the usual practice is the administration of single injections of 600,000 units each at one to three day intervals until a total of 10 to 12 million units has been given.

Penicillin alone is satisfactory for the treatment of most patients with neurosyphilis and certainly for the majority of those with clinical forms other than parenchymatous neurosyphilis (tabes dorsalis or general paresis). In many patients with tabes dorsalis, penicillin alone is not completely satisfactory in the relief of symptoms, and the proper management of such patients is often a complex medical procedure, necessitating specialized methods of approach (fever therapy, especially with induced tertian malaria, and neurosurgical procedures for the relief of gastric crises). In one particular complication of tabes dorsalis, namely, primary optic atrophy, evidence is not yet available as to the efficacy of penicillin therapy in bringing about arrest of the atrophic process. Many observers still feel strongly that treatment in such patients should consist of fever therapy, with induced tertian malaria,

combined with penicillin administration. In patients with general paresis, the use of penicillin for the initiation of treatment creates about a 10% risk of serious clinical Jarisch-Herxheimer reactions, which may be avoided by initiating treatment with fever therapy, penicillin therapy being delayed until the patient has had two or three paroxysms.

It is not quite accurate to use the word "cure" in speaking of the treatment of neurosyphilis. This word may be applied only to the inflammatory component of the lesion, or, to put it differently, to the possible "cure" of the underlying treponemal infection. A cure of symptoms and signs produced by actual degeneration within the nervous system is not possible. From the laboratory point of view, the efficacy of treatment in neurosyphilis may be measured by the cell count and the protein content in the spinal fluid. In 95% of all neurosyphilitic patients treated with penicillin, both the cell count and protein content usually promptly (within six months) become normal and usually remain so. Having once reverted to normal, a subsequent increase in cell count or protein content may be interpreted as relapse of the inflammatory component of the neurosyphilitic lesion and as an indication for retreatment. This is the so-called Dattner-Thomas concept of "active" versus "inactive" spinal fluid and is thoroughly documented in the literature. Patients who are hypersensitive to penicillin G may usually be satisfactorily treated with either fever therapy or one of the nonallergenic penicillins, such as penicillin O. Metal chemotherapy in such patients or, indeed, in neurosyphilis in general, has been almost completely abandoned. The broad spectrum antibiotics, aureomycin, oxytetracycline and chloramphenicol, are less effective than penicillin.

VITAMIN B GIVEN INTRAVENOUSLY

To the Editor:—*Is there any explanation for the fact that a chronically fatigued woman feels more energetic following intravenous injection of vitamin B? This increased energy and well-being is said to last for a week or longer. The woman is about 40, has four children, is socially prominent, was athletic, and is in apparent good health. It is my feeling that this result has more of a psychic than a physiological basis.*

M.D., Ohio.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—The good effect obtained from the administration of vitamin B once a week probably has a psychic basis. It is unlikely that there is a deficiency of this substance in a healthy woman who is on a well-balanced diet.

Answer.—The increased sense of well-being described by the patient is probably psychogenic. It is doubtful whether there is any clinical indication for intravenous administration of vitamin B other than the presence of wet beriberi. Sensitization reactions following intravenous administration of thiamine chloride have been observed, some severe enough to cause death.

SINUS BRADYCARDIA

To the Editor:—*An 86-year-old woman, well and happy, had the pulse rate of complete heart block, 40 beats per minute. On Jan. 3, 1953, she had an acute cold, with difficulty in breathing, and her blood pressure was 190/110. I was surprised to find the pulse of heart block absent, the rate being 64. She has long since recovered from the cold and is again well. I have never heard of a heart block adjusting itself to a normal heart beat. Is this an unusual case? The patient has been receiving no medication that would affect her heart condition.*

M.D., Iowa.

Answer.—Sinus bradycardia with a pulse rate of 50 to 60 beats per minute is common in many normal persons of both sexes and in all age groups. Occasionally, as on first awakening in the morning, the rate may fall to between 40 and 50 in such persons. An electrocardiogram is usually necessary to establish the presence and degree of heart block. For example, a heart rate of 40 might be associated with an auricular rate of 80, with a 2:1 atrioventricular block, or, rarely, it may be due to atrioventricular nodal rhythm. Complete heart block ordinarily results in an independent ventricular rate of 35 or below. In older persons, it is usually caused by coronary heart disease, although angina pectoris, congestive failure, or myocardial infarction need not be associated as part of the clinical picture. Temporary complete heart block is occasionally seen accompanying an infarction of the posterior wall of the left ventricle. It may also occur with narrowing of the vessels supplying the junctional tissues with blood when the atrioventricular block varies with the activity of the person and the state of the circulation.

AZOOSPERMIA

To the Editor:—*I have been treating a 30-year-old man for sterility. I have given him vitamin E (100 mg.) twice daily and testosterone (25 mg.) twice a week. Examination of the seminal fluid at the beginning of treatment revealed no sperms, and recent examinations revealed no sperms. This patient had mumps when a child. One testicle appears normal in size and the other is slightly atrophied. What suggestions can you make for treatment?*

B. C. Kappmeyer, M.D., Hamilton, Ill.

Answer.—To determine the proper treatment in this case, certain tests should be made to establish a diagnosis. In azoospermia, such as appears here, bilateral testicular biopsy of the serialized type should be performed. If the biopsy material, taken from several areas of each testicle, shows normal spermatogenesis, a diagnosis of bilateral absence or obstruction of the avenues of sperm outlet is justified. If the biopsies show temporary arrest due to pituitary insufficiency, injections of a potent pituitary product might be beneficial. If, on the other hand, the biopsies show marked peritubular fibrosis or marked diminution in the number of germ cells, treatment is not likely to be of any avail. Vitamin E, when given in sterility, is used on psychological grounds, only. The importance of following the ordinary hygiene of living should be stressed.

POSSIBLY NEUROGENIC HYPOGLYCEMIA

To the Editor:—*The question of Dr. Joel Peterson of St. Paul, in* The Journal *for April 18, 1953, page 1463, interested me greatly. The history of undue fatigue, nervousness, and abnormal craving for sweets, with a normal fasting blood sugar level, certainly indicates hyperinsulinism or so-called neurogenic hypoglycemia. A six hour glucose tolerance test would no doubt show the hypoglycemia. Regardless of the outcome of the test, the symptoms call for a diet test. Improvement with the proper diet should be spectacular in one or two weeks. This diet is one high in protein, low in carbohydrates, and high in fat, with no sweets or caffeine and with frequent feedings. The diet recommended by Dr. Seale Harris is still the best. If all physicians would read the work of Dr. Seale Harris on dysinsulinism and hyperinsulinism (J. A. M. A.* **83:***729 [Sept. 6] 1924; Ann. Int. Med.* **10:***514 [Oct.] 1936) as well as "Body, Mind, and Sugar," by Dr. Abrahamson (New York, Henry Holt & Company, Inc., 1951), thousands of persons would not have to go through what I did. During three years of severe illness I was examined by 14 specialists and 3 nationally known clinics before a diagnosis was made by means of a six hour glucose tolerance test, previous diagnoses having been brain tumor, diabetes, and cerebral arteriosclerosis. Seeing the six hour cure, I found the answer in Dr. Seale Harris's diet and immediately recovered.*

Since then I have used this hard earned knowledge in diagnosing and curing the condition in numerous patients, in some of whom the blood sugar level, like mine, at times dropped to 50 mg. per 100 cc.

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